


# Cost-Effectiveness of Primary Endocrine Therapy Comparing against Surgery as the Initial Treatment Strategy in Older Women with Primary Breast Cancer

Submitted by

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**Dedication**

“By the name of Allah, the most merciful, the most compassionate”

This thesis is dedicated to:

My kind parents,

My father who put his trust on me, supported me, and took all the risks needed to achieve my dream,

My mother who supported me and gave me the strength to accomplish my dream,

And

My lovely sisters and brothers,

**Abstract**

**Background**

Breast cancer is highly prevalent in older women. Although surgery is the main initial treatment for younger population, research has demonstrated that older women with primary breast cancer have different tumour biology, comorbidities, and patient preferences from younger patients, and hence may benefit from primary endocrine therapy (PETx), such as Tamoxifen and aromatase inhibitors (AIs). However, there is no cost-effectiveness study that compares the use of different treatment strategies in older women.

**Aim of study**

This study aimed to evaluate the clinical and cost-effectiveness of using PETx against surgery as the initial treatment strategy in older women with primary breast cancer.

**Methods**

This research included four stages. First, a retrospective cohort study was conducted to describe the treatment pathways, and evaluate the effectiveness and costs associated with using different treatment strategies by using a longitudinal database of 1,759 older women, who were diagnosed with primary breast cancer at ages over 70 years old in breast cancer units in Nottingham. Regression analyses, including survival analysis and generalised linear model, were used to identify the covariates, the predict death rates and costs, respectively.

Second, a systematic review of economic evaluation studies was conducted using NHS Economic Evaluation Database, Cochrane Library, Ovid Medline, PubMed, and EMBASE to identify full economic evaluations that compared different treatment strategies in postmenopausal women with primary breast cancer. Quality and modelling methodologies of the included studies were assessed and summarised.

Finally, a Markov model was conducted from the systematic review to estimate the lifetime costs and quality adjusted life year (QALYs) associated with the use of PETx as against surgery in a hypothetical cohort of older women with primary breast cancer and ER-positive status. The analysis took the UK NHS perspective with a lifetime horizon. Transition probabilities were estimated using parametric survival models derived from the longitudinal database. Resource use and costs were assessed in British pounds of the year 2014 using the longitudinal database. Utilities were derived from literature, including Prescott *et al.* (2007) (1), Fallowfield *et al*. (1994), and Peasgood *et al*. (2010)(2). Both costs and outcomes were discounted by 3.5% annually. A subgroup analysis was conducted for patients with higher oestrogen receptor content (H-score >250 out of 300). PSA was conducted and aggregated results were presented in cost-effectiveness plane and cost-effectiveness acceptability curve. Sensitivity analysis was also conducted to investigate the impact of uncertain parameters and model assumptions.

**Results**

Retrospective analysis of the cohort study found that most patients received surgery (n=350; 52.08%) or PETx (n=322; 47.92%) as the initial treatment strategy. The most common adjuvant therapy was endocrine therapy (n=164; 46.86%). Comparing to those received surgery as an initial treatment, patients who received PETx had a significantly higher adjusted risk of breast cancer-related death (HR: 2.15; 95%CI: 1.03, 4.46), and lower costs (mean difference: -£3558.87; 95%CI: -£4018.11, -£3105.39).

Overall, 29 economic evaluations were included from the systematic reviews and studies that assessed surgery and none assessed PETx as the initial treatment. Most of the included economic studies used a Markov model with lifetime horizon and one-year cycle length. Nine studies which included subgroup analysis for older women

(over 65 years old) used similar economic models and transition states to those that were used for younger women (50 to 65 years old) with primary breast cancer. The key disease-related health states were disease-free, recurrence, and death. Recurrence was mostly separated into locoregional and distant recurrence. These findings were used to design a Markov model in the following decision modelling.

In the base-case analysis of decision analytical modelling, the deterministic results showed that patients who received PETx as the initial treatment had lower costs and QALYs compared with patients who received surgery; the mean ICUR was £194 per QALY. However, for patients with H-score >250, PETx was associated with higher costs and lower QALYs; the mean ICUR was -£1849 per QALY.

In the probabilistic sensitivity analysis, PETx was associated with lower costs and QALYs. The mean ICUR was £363 per QALY, 95%CI: -6014.99, 5,756.86). However, for patients with H-score >250, PETx was associated with higher costs and lower QALYs. The mean ICUR was -£390.67 per QALY (95%CI: -7,295, 7776.54). The probability of PETx being cost-effective in a situation where the decision-maker is willing to accept (WTA) £21,000 per QALY was 24%. In the subgroup analysis, PETx was associated with slightly lower QALYs and higher costs. The probability of PETx being cost-effective in a situation where the decision-maker is willing to accept £21,000 per QALY was 43%.

**Conclusion**

The main findings from this study showed that PETx was not cost-effective compared to surgery. However, this study was mainly based on the effectiveness and cost from a single observational study in a secondary care setting, and other information (evidence) that may bias the effectiveness and cost estimates, including frailty status, adherence, comorbidities, and other unmeasured confounders were not recorded, and

thus, may bias the cost-effectiveness results. Future research is recommended to collect further information on patients' characteristics, including frailty, adherence, and adverse events that may influence the cost-effectiveness results. Moreover, collecting detailed estimation of the resource use in order to provide an accurate estimate for costs.

## List of publication

### Peer-reviewed conference presentations

Mousa R, Chen LC, Cheung KL. An evidence-based model design to inform the cost-effectiveness evaluation of primary endocrine therapy and surgery for older women with primary breast cancer. Value Health. 2014;17(7): A638

Mousa R, Chen LC, Cheung KL. An evidence-based model design to inform the cost-effectiveness evaluation of primary endocrine therapy and surgery for older women with primary breast cancer. Future Oncology. 2015; 11(4s): 21

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## List of abbreviations

| | |
|---|---|
| AI | Aromatase Inhibitor |
| BC | Breast cancer |
| BCTx | Breast conservative therapy |
| BTx | Biological Therapy |
| CB | Clinical benefit |
| CBC | Contralateral breast cancer |
| CE plane | Cost-effectiveness planes |
| CEA | Cost-effectiveness analysis |
| CEAC | Cost-effectiveness acceptability curve |
| CR | Complete response |
| 95%CI | 95% confidence interval |
| CT | Computerised Tomography |
| CTx | Chemotherapy |
| CUA | Cost-utility analysis |
| DES | Discrete event simulation |
| DF | Disease free |
| DR | Distant recurrence |
| EE | Economic Evaluation |
| EQ-5D | European Quality of Life-5 Dimensions |
| ER | Oestrogen receptor |
| ETx | Endocrine therapy |
| EU | European Union |
| FEC | Fluorouracil (5FU), Epirubicin and Cyclophosphamide |
| GPs | General practitioners |
| GLM | Generalized linear regression |
| Gy | Gray |
| HER2 | Human Epidermal Growth Factor Receptors |
| HR | Hazard ratio |
| HSUVs | Health state utility values |
| ICER | Incremental cost-effectiveness ratio |
| ICUR | Incremental cost-utility ratio |
| IQR | Interquartile range |
| LR | Local recurrence |
| LRR | Locoregional recurrence |
| LYGs | Life year gained |
| MDT | Multidisciplinary Team Meeting |
| MNL | Multinomial Logistic |
| NE | Northern East |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NP | No Progression |
| NW | Northern West |
| OR | Odds ratio |
| OS | Overall survival |
| PD | Progressive disease |
| PETx | Primary endocrine therapy |
| PR | Partial response |
| PRs | Progesterone receptors |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality adjusted life year |
| QoL | Quality of life |
| RCTs | Randomized controlled trials |

| | |
|---|---|
| RF | Relapse free |
| RR | Relative Risk |
| RTx | Radiotherapy |
| SD | Standard deviation |
| SD | Stable disease |
| SE | Southern East |
| SG | Standard Gamble |
| SLND | Sentinel Lymph Node Dissection |
| SW | Southern West |
| TTO | Time Trade-Off |
| Tx | Treatment |
| UK | United Kingdom |
| USA | United State |
| VAS | Visual Analogue Scale |
| WLE | Wide Local Excision |
| WTA | Willingness to accept |
| WTP | Willingness to Pay |

# Chapter 1. Literature review, aims and objectives

## 1.1. Background

The demand for clinical care in older women with breast cancer is increasing both globally and in the UK due to the high prevalence of breast cancer in older women (3,4). Currently, there is a lack of robust (i.e. large RCTs) clinical studies conducted in older women with primary breast cancer (5).

Moreover, evidence is emerging to suggest that breast cancer in older women is associated with less aggressive tumour biology, which is associated with better prognosis in terms of disease progression and survival compared with younger populations. Thus, older women may benefit from less aggressive non-surgical treatments, including PETx (6). Given the increase in cost pressure for treating older women with breast cancer, economic evaluation is deemed necessary to identify the cost-effectiveness of these treatment strategies within the limited budget available to the UK NHS.

This chapter aimed to describe the epidemiology of different types of breast cancer in both younger and older population, and their impact on overall mortality focusing specifically in primary breast cancer. In addition, it aimed to review evidence from literature, including RCTs and observational studies in older women with primary breast cancer to establish background knowledge of clinical practice and highlight the lack of robust clinical study conducted on older women with primary breast cancer. This was followed by describing the challenges in treating primary breast cancer in older women, including the impact of age on tumour biology, frailty, comorbidities, side effects, and patients' preferences. Finally, the reasons behind the increasing health care expenditure, mainly the aging population and cancer treatment were highlighted to introduce the role of economic evaluation in prioritizing resource allocation. The complexity of the definition and terminology for age specifically the definition of older

people were also discussed. This is due to the fact that this PhD project investigated treatment strategies in older women, and hence, different definitions for old age were considered.

## 1.2. Increasing demands for care in older women with breast cancer

### 1.2.1. Epidemiology

Breast cancer is the most prevalent cancer among female globally and in the European Union (EU) (3). It accounted for 38% (5.2 million out of 15.28 million) and 41.4% of female breast cancer between 2004 and 2008 (5-year prevalence) worldwide and in Europe, respectively (3). Breast cancer is also by far the cancer with the highest incidence worldwide and in the EU, with around 1.7 million new cases registered worldwide out of 6.6 million (25%) of all female cancer cases worldwide in 2012 (7), of which 67% (n=1.12 million) of the 1.7 million female patients newly diagnosed with breast cancer were aged over 50 years old and 30% (n=0.5 million) aged over 65 years old (8). In western EU countries, 156,045 new cases were registered out of 490,181 (31.8% of all female breast cancer cases) in 2012 (9). Variation in incidence between countries may partly be explained as being due to different prevalence of risk factors and the use of screening programmes (10,11).

Similar to the global trend, breast cancer is the most common cancer diagnosed among female (all ages combined) in the UK. In 2013, 44,540 new breast cancer cases were registered comprising 31.2% of all female cancer registrations in the UK (4), of which 80% of female patients diagnosed with breast cancer were aged over 50 years old and 47% aged over 65 years old (4). The incidence rate for breast cancer (cases per 100,000 females) has increased by 5.5% in the past decade, from 161.0 in 2004 to 169.8 in 2013 (4).

The median age of the UK population increased from 35.4 years in 1985 to 39.7 years in 2010 (12). Moreover, the proportion of older people over 65 years in the UK has increased from 15% in 1985 to 17% in 2010. Given that breast cancer is common in older women and the aging population increases with time, the percentage of older women who are diagnosed with breast cancer will increase. In fact, the breast cancer

incidence rate has increased in the UK in all age groups since 1970 (4). This may partly be explained as being due to the implementation of the NHS England Breast Screening Programme in 1988, which offered routine mammographic screening to each woman in the UK aged 50-64 once every three years. In 2000, the Programme extended the age limit to include women up to 70 years old (13); consequently an increasing number of women received screening.

Since the risk of breast cancer increases with age, along with the increasingly aged population in the UK and the extended age limit in Breast Screening Programme, it is expected that more cases of breast cancer in its early stage will be detected in the UK (14,15) and the incidence of breast cancer in older patients, will continue to rise (12,15), consequently, the demands for treatment of older women with primary breast cancer will increase.

### 1.2.2. Risk factors

Incidence of breast cancer has found to be associated with age, female sex, age at menopause, the level of sex hormones at post-menopause, hormone-replacement therapy, and family history of breast cancer (11,16). Similar to the global epidemiology, the majority of breast cancers were diagnosed in females (99.3% in 2013) in the UK (4). The breast cancer incidence rates were higher in the older age groups; in England in 2013, the incidences for 50-59, 60-69, 70-79, 80-89 years groups were 557, 770, 755, and 891 per 100,000 population, respectively (4).

Although menopause is not associated with increasing the risk of breast cancer, breast cancer incidence is strongly associated with the age at menopause (17). In addition, postmenopausal women are commonly using hormone-replacement therapy to manage their menopausal symptoms (18), and the longer duration of exposure to the hormonal replacement therapy increases the risk of breast cancer (18). Furthermore,

breast cancer risk for postmenopausal women was found to be positively associated with the level of oestrogen in postmenopausal women, but this association was not significantly in premenopausal women (19).

### 1.2.3. Distinct pathology and biology characteristics of breast cancer in older women

#### 1.2.3.1. Tumour stage

After diagnosis, the breast cancer can be categorised into four different stages, including primary (stage I-II), locally advanced (stage III), or secondary breast cancer (stage IV) by applying a universally accepted tumour node metastasis (TNM) cancer staging scheme that categorises cancer based on the size of the tumour (T), whether the tumour has spread to other lymph nodes (N), and whether the tumour has spread to other parts of the body (M) (Table 1.1.). Primary breast cancer is the most common breast cancer in the UK, in 2013, the majority (84%) of breast cancer patients who were diagnosed in England had primary breast cancer (44% stage I, 40% stage II), 10% were in stage III, and 6% in stage IV (20). Tumours at stage I/II are potentially curable and surgery is generally the standard initial treatment, as compared to stage III/IV (Table 1.2.).

**Table 1.1. Tumour node metastasis (TNM) cancer staging scheme (21)**

| **T - Primary Tumour** |
|---|
| **TX.** Primary tumour cannot be assessed |
| **T0.** No evidence of primary tumour |
| **Tis.** Carcinoma in situ |
| **Tis (DCIS).** Ductal carcinoma in situ |
| **Tis (LCIS).** Lobular carcinoma in situ |
| **Tis (Paget).** Paget disease of the nipple with no tumour |
| **T1.** Tumour 2 cm or less in greatest dimension |
| **T1mic.** Microinvasion 0.1 cm or less in greatest dimension |
| **T1a.** More than 0.1 cm but not more than 0.5 cm in greatest dimension |
| **T1b.** More than 0.5 cm but not more than 1 cm in greatest dimension |
| **T1c.** More than 1 cm but not more than 2 cm in greatest dimension |
| **T2.** Tumour more than 2 cm but not more than 5 cm |
| **T3.** Tumour more than 5 cm |
| **T4.** Tumour of any size with direct extension to chest wall or skin only as described in T4a to T4d |
| **T4a.** Extension to chest wall |
| **T4b.** Oedema or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast |
| **T4c.** Both 4a and 4b, above |
| **T4d.** Inflammatory carcinoma |
| **N - Regional Lymph Nodes** |
| **NX.** Regional lymph nodes cannot be assessed (e.g., previously removed) |
| **N0.** No regional lymph node metastasis |
| **N1.** Metastasis in movable ipsilateral axillary lymph node(s) |
| **N2.** Metastasis in fixed ipsilateral axillary lymph node(s) or in clinically apparent ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis |
| **N2a.** Metastasis in axillary lymph node(s) fixed to one another or to other structures |
| **N2b.** Metastasis only in clinically apparent M internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis |
| **N3.** Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement; or in clinically apparent ipsilateral internal mammary lymph node(s) in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| **N3a.** Metastasis in infraclavicular lymph node(s) |
| **N3b.** Metastasis in internal mammary and axillary lymph nodes |
| **N3c.** Metastasis in supraclavicular lymph node(s) |
| **M - Distant Metastasis** |
| **MX.** Distant metastasis cannot be assessed |
| **M0.** No distant metastasis |
| **M1.** Distant metastasis |

**(Continue Table 1.1.)**

| Tumour stage | tumour grade | Nodal status | Metastasis |
|---|---|---|---|
| **Stage 0** | Tis | N0 | M0 |
| **Stage I** | T1 * | N0 | M0 |
| **Stage IIA** | T0 | N1 | M0 |
| | T1 * | N1 | M0 |
| | T2 | N0 | M0 |
| **Stage IIB** | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| **Stage IIIA** | T0 | N2 | M0 |
| | T1 * | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1, N2 | M0 |
| **Stage IIIB** | T4 | N0, N1, N2 | M0 |
| **Stage IIIC** | Any T | N3 | M0 |
| **Stage IV** | Any T | Any N | M1 |
| Note:* T1 includes T1mic. | | | |

**Table 1.2. Types and categories of breast cancer**

| Type of breast cancer | Other names | Definition |
|---|---|---|
| Primary | Early stage, operable, or stage I/II breast cancer | Cancer is localised to breast tissue or lymph nodes in the armpit |
| Locally advanced | Stage III breast cancer | Cancer is localised to the breast tissue, but has a large tumour size >5 cm |
| Secondary | Metastatic or stage IV breast cancer | Cancer spread to other organs such as liver or bone |

Although population-based studies which evaluated the variation in the breast cancer stages among different age groups in the UK are limited, the breast cancer stage determined at diagnosis is likely to be related to the timing of detecting cancer or accessibility to screening programmes (22,23). A population-based study analysed 17,836 women who were diagnosed with breast cancer during 2006 to 2009 in East of England. Comparing to women aged 65-69 years old, all the age ranks of older women >70 years old (70-74, 75-79, 80-84 and >85 years) are more likely to be diagnosed with advanced stage of the disease (odds ratios: 1.21, 1.46, 1.68, and 1.78, respectively, $P<0.001$) (22). This may partly be attributed to the limited access to screening programmes in older women (>73 years old), and consequently more older women were diagnosed at advanced stage of breast cancer (23).

Although older women may be diagnosed with a more advanced stage of breast cancer than younger population, overall, stage I/II is still the most common diagnosed stage among older women with breast cancer. Data from the Netherlands Cancer Registry between 2000 to 2005 showed that for women diagnosed with breast cancer at age 70-79 years, the majorities were diagnosed at stage I/II (82%), followed by III (10%), and stage IV (5%). For those diagnosed at age over 80 years, 77% were at stage I/II, followed by stage II I (15%), and stage IV (8%) (23).

#### 1.2.3.2. Tumour biology

Measuring the expression of tumour biomarkers is important since their expression are associated with particular clinical outcomes; and hence guide the responding to a particular treatment (24). Tumour biomarkers for breast cancer, including ER, progesterone receptors (PRs), and human epidermal growth factor receptors (HER2) are expressed at various levels on breast cancer cells in different age groups. The cut-off of the percentage of breast cancer cells stained is used to define positivity and negativity of receptors in tumour cells. Levels of expression of ERs and PRs are measured using the immunohistochemistry (IHC) method (25-27), which derives a histological score (H-score) in a range of 0 to 300 that measures the intensity and distribution of ERs and PRs, i.e. the overall percentage of tumour cells expressing ERs or PRs stained by IHC. The H-score measured using the following equation, where categories refers to the intensity of staining (i.e. no staining=0, weak staining=1, moderate=2, strong=3) (25).

H-score=(% of cells stained at category intensity 1*1)+(% of cells stained at category intensity 2*2)+(% of cells stained at category intensity 3*3).

Although there is no definitive cut-off for ER and PR positivity, 1% of tumour cell staining was shown to correlate with the clinical outcome, i.e. disease-free and overall survival (24). Therefore, the American Society of Clinical Oncology guideline recommends that the cut-off for ER and PR positivity should be higher than 1% of tumour cell staining (27).

Research has demonstrated that older patients have breast tumours which are more likely to be ER and/or PR positive, but HER2 negative, when compared with younger patients, with these features being associated with less aggressive tumours (28-31). Several studies compared the tumour characteristics amongst different age groups (6,28-31). Two of the largest studies that included 307,115 and 24,935 women with

breast cancer from the San Antonio database and the Surveillance, Epidemiology, and End results (SEER) registry in the United States (USA), respectively, with the former study analysed the tumour characteristics across different age groups, including 55-64 years old, 65-74 years old, 75-84 years old, and 85 years old or older (30), whereas the latter analysed the tumour characteristics specifically for patients aged ≤35 and 50-55 years (28).

Both studies showed that the older the patient, the more likely for the patient to have tumours containing oestrogen-positive and progesterone-positive receptors, and less likely to have tumour containing HER2-positive receptors. The ER-positive status were found in 83%, 87%, 90%, 91% of patients aged 55-64 years old, 65-74 years old, 75-84 years old, and 85 years old or older, respectively. While the PR-positive status were found in 57%, 63%, 64%, 66% of patients aged 55-64 years old, 65-74 years old, 75-84 years old, and 85 years old or older, respectively. HER2-positive status were found in 17%, 15%, 11%, 10% of patients aged 55-64 years old, 65-74 years old, 75-84 years old, and 85 years old or older, respectively (28,30).

Another study analysed the biological characteristics of 1,758 women with primary breast cancer over 70 years old who were managed in the breast cancer unit at Nottingham and followed for 37 years, and compared this cohort with a younger cohort (individuals <70 years old) of patients with breast cancer (6). In agreement with the previous studies, this study also showed that the proportions of women over 70 years old had tumours with ER-positive (70.1% vs. 66.7%, P=0.04), PR-positive (56.7% vs. 43.3%, P=0.01), ER-negative, (29.9% vs. 33.3%, P=0.04), HER2-positive (7.7% vs. 8.2%, P=0.4), lower tumour grade, axillary stage, and tumour size are significantly different to their younger counterparts (6). Higher expression of ER-positive and PR-positive, and low expression of HER2-positive were associated with better disease progression and survival in older women (6,28,30). This study showed that positive

expression of ERs was associated with significantly higher 5-year breast cancer-specific survival (93% vs. 76%, P=0.002) and disease-free survival (80% vs. 63%, P≤0.001) compared with negative-ER status. However, the expression of HER2 was associated with lower breast cancer-specific survival (75% vs. 90%, P≤0.01) and disease-free survival (70% vs. 76%, P≤0.01) compared with the absence of HER2 expression (6). Therefore, assessing tumour biology is important when physicians consider treatment for breast cancer.

Given the higher incidence of ER status in older women with primary breast cancer with around 80% of primary breast cancers in older women over 70 years were ER and its impact on the treatment decision (26), the percentages of this biological marker and its influence on treatment selection were reviewed in detail in this chapter. The strength of ER positivity (25,26) has been shown to increase with age. Moreover, the proportion of patients who had an H-score over 200 were 4%, 5%, 21%, and 42% in patients who were <=35, >35-50, >50-70, >70 years old, respectively (26).

Emerging results from the literature showed that higher ER positivity was associated with better disease-free and overall survival in postmenopausal and older women (32). A retrospective analysis of 563 postmenopausal patients with ER-positivity receiving adjuvant endocrine therapy (ETx) following surgical procedure, who were initially treated between 1974 and 2004, revealed that the 10-year survival rates were 41%, 71%, 67%, and 84% for H-scores ≤50, 51-100, 100-200, and >200, respectively (P<0.001). However, 10-year disease-free survival rates were 28%, 83%, 73%, 84% for H-scores ≤50, 51-100, 100-200, and >200, respectively (P<0.0001) (32).

### 1.2.4. Breast cancer impacts on survival in older women

Different outcome indicators have been used in analysing breast cancer survival, including overall, breast cancer, and relative survival rates (33). The overall survival

(the probability of patients who remained alive after diagnosis) considers all-cause mortality, including breast cancer and non-breast cancer related causes as the endpoint of measure. Breast cancer survival rate considers only death from the breast cancer as the endpoint. The relative survival is the ratio of the overall survival rate divided by the expected survival rate for a group of people in the general population similar to the patient group with respect to race, sex, and age (33). As breast cancer patients get older, there is a higher risk that the patients may develop other diseases alongside breast cancer, and hence the all-cause mortality rates will increase and the overall survival rates reduce (30,31).

With the advance in the developments of treatment strategies, the survival rate of patients with breast cancer has been markedly increased during the 40-year period between 1971 and 2011 (34). In Europe, the 5-year relative breast cancer survival rate was 79% between 1997 and 2002 and has been increased to 82% between 2004 and 2009. The highest survival rates between 2004 and 2009 were in France, Finland, Belgium, Sweden, Norway, and Iceland (ranged from 86% to 87%) (11). Similar to the majority of European countries, the 5-year relative survival rate of breast cancer in the UK increased from 75% to 81% in the same period (11).

Patient's age and stage of cancer at diagnosis are highly associated with breast cancer survival. Compared to other stages of breast cancer, women diagnosed with primary breast cancer in the UK have the highest one-year relative survival rate (dividing the proportion of patients who still alive for one year or more after being diagnosed with breast cancer by the proportion of people of the same age and sex who don't have breast cancer). In 2012, it was reported that the proportion of women in England with breast cancer survived for one year or more, was higher for those diagnosed at stage I/II (99.6%), followed by locally advanced (96.8%) and metastatic (67.1%) breast cancer. The one-year relative survival also varied with age; the survival rate declined

with the increase of age ranks from 15-49 (98%) to 50-59 (97.8%), 60-69 (97.6%), 70-79 (94%), 80-89 (91%), and 90-99 (85%) years old (35).

### 1.3. Efficacy, effectiveness, and safety of treatment strategies for older women with primary breast cancer

A variety of treatment strategies is available for treating primary (stage I/II) breast cancer, including primary treatment followed by adjuvant treatments (36). Surgical treatment remains the main curative method and has been recommended as the first-line primary treatment (i.e. the initial treatment for patients with primary breast cancer regardless of age) by several guidelines, including the National Institute for Health and Care Excellence (NICE) guideline (36) . Surgery applied to patients with breast cancer can be categorised as mastectomy, which involves the removing of the entire breast (37,38), or a less invasive breast conservative therapy (BCTx), which involves removing part of the breast tissues (37). Either the breast lump with part of the normal breast tissue (lumpectomy or wide local excision [WLE]) or a quarter of the breast cancer may be removed (quadrantectomy).

Adjuvant therapy is an additional treatment that is used after surgery to eliminate any hidden cancer cells; it may be provided through local treatment in the form of systemic therapy (i.e. ETx), chemotherapy [CTx], or biological therapy [BTx]) or radiotherapy (RTx) (39). There are two major classes of ETx that have been used for treating breast cancer based on their anti-osteogenic effects, including tamoxifen, and aromatase inhibitors (AIs) (i.e. anastrozole, letrozole, and exemestane (40). Tamoxifen is considered as an adjuvant therapy for the treatment of pre- and postmenopausal women with primary ER-positive breast cancer (40); It has dual oestrogen antagonist and agonist effects. The anti-oestrogenic activity of tamoxifen originates from binding to the oestrogenic receptor (ER), and hence it blocks the oestrogen from binding to ERs in breast cancer cells, which consequently inhibits the growth of breast cancer

cells (40). AIs are alternative options to tamoxifen in postmenopausal patients in whom tamoxifen is contraindicated or who are intolerant of tamoxifen. AIs block the aromatase enzyme in the fat tissue that is responsible for producing oestrogen in postmenopausal women (38). RTx works by generating free radicals that damage the DNA chain of cancerous cells, thus leading to their cellular death (41). CTx blocks the steps in the synthesis of DNA of the tumour cell (41). BTx including trastuzumab, are monoclonal antibodies that target the HER2 receptor on the breast cancer surface (38,42,43).

Alternative non-surgical treatments (i.e. PETx, primary RTx) or no treatment at all may be considered when patients are unsuitable to receive surgery due to different tumour biology, fitness to surgery, or patients' choices (44). PETx and primary RTx refer to the use of ETx and RTx as the sole initial treatment, respectively. Clinical trials which assessed the efficacy of PETx have mainly used tamoxifen (5), although AIs could be preferable in the neoadjuvant, adjuvant, and metastatic settings (45). However, the current treatment guidelines for breast cancer are mainly based on evidence from a younger population. Although some studies reported the evidence in stratified age groups, the current evidence for the efficacy (RCT data) of different treatment strategies for older women is limited in terms of small sample size.

Subsequent lines of treatments (including second, third, fourth line,..etc) are offered for patients who experienced breast cancer progression, including locoregional or metastatic progression, following receiving the initial treatments.

### 1.3.1. Different types of surgery in older women with primary breast cancer

BCTx is associated with fewer cosmetic issues, and it could achieve the same overall survival rate compared with mastectomy in patients with primary breast cancer across different age groups.

The European Organisation for Research and Treatment of Cancer (EORTC) trial (n=236) compared modified radical mastectomy (n=120) against lumpectomy plus tamoxifen (n=116) in older (≥70 years) women with primary breast cancer, and found no significant difference in overall mortality between both treatment groups, although patients in the mastectomy group had a higher rate of metastasis (28% vs. 13%, P=0.006) (46).

However, BCTx is not indicated for those patients who have multicentric diseases, have any large tumour tissue that is unapproachable by the BCTx, are unfit for the postoperative RTx, or do not prefer this type of surgery (47).

Since breast cancer could be spread to the axillary lymph node, two approaches are clinically available to test and remove the lymph nodes (39). Axillary lymph node dissection (ALND; or axillary clearance) involves removing large numbers of the lymph nodes during the surgery (either mastectomy or BCTx) and testing those lymph nodes under the microscope (39).

ALND is now replaced by a less invasive procedure - sentinel lymph node biopsy (SLNB) which involves an injection of a radiocontrast dye in the area of breast cancer and then 1 to 3 sentinel nodes are removed and tested for the presence of breast cancer cells. If cancer cells are found, a further ALND should be carried out to remove all the lymph nodes (48).

NICE guideline recommended the preoperative assessment of the axilla using ultrasound evaluation of the axilla (mammogram) to be performed for all patients, and if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered (49). If the ultrasound-guided needle sampling showed positive, i.e. palpable lymph node, an axillary clearance is carried out at the same time

of the breast surgery. If it tested negative a SLNB is conducted at the same time of the breast surgery. However, if the SLNB is positive, further second operation, i.e. axillary clearance is required. Staging of the ipsilateral axilla is essential for deciding which local and systemic treatments are subsequently required. The axilla can be staged using axillary surgery carried out at the same time as the breast surgery (36).

### 1.3.2. Primary endocrine therapy in older women

PETx could be a reasonable option for older women with primary breast cancer (50), since such older women have more ER-positive cancer cells than younger patients, and hence ETx can be used as a primary treatment for older breast cancer patients who are unfit for, or refuse surgery (44).

#### 1.3.2.1. Evidence from observational studies

The treatment effect of PETx has been studied in a systematic review by Morgan *et al.* (2014) (5,51) which aimed to summarise PETx efficacy and effectiveness from RCTs and observational studies conducted in older women with primary breast cancer. This systematic review included 29 cohort studies, which were published as full texts, 18 studies were conducted in the UK (52-69). Among the 29 studies, 20 studies investigated the effectiveness of PETx alone (i.e. without a comparator), among the eight studies which compared the effectiveness of PETx against a comparator, four studies included surgery (55,61,69,70). Overall, these 29 studies enrolled very small numbers of patients (27 to 235) and had a short follow-up duration, which ranged from 1 to 202 months.

#### 1.3.2.2. Evidence from randomised controlled trial

Six RCTs that had been conducted in older women over 70 years old with primary breast cancer, who were fit for surgery during 1984 and 1992 (46,50,71-74). These trials included 131 to 474 participants with follow-up duration ranging between 3 to

12.7 years. Three RCTs compared the use of PETx against 'surgery plus adjuvant ETx' (72-74), while the other three studies compared the use of PETx against surgery (46,50,71).

Pooled overall survival did not show any significant difference in comparing surgery against PETx (HR: 0.98; 95%CI: 0.81, 1.20; P=0.85) and comparing surgery plus adjuvant therapy against PETx (HR: 0.86; 95%CI: 0.73, 1.00; P=0.06). Among all studies, two studies reported progression-free survival and there was a significantly lower risk of progression in comparing surgery against PETx (HR: 0.55; 95%CI: 0.39, 0.77; P=0.0006) (46) and for comparing surgery plus adjuvant ETx against PETx (HR: 0.65; 95%CI: 0.53, 0.81; P=0.0001) (74).

Although there have been RCTs conducted specifically in older women with primary cancer, the issues around internal and external validities limited their usefulness as a source of evidence to inform the treatment efficacy in older women with breast cancer. Except for one study (73), the other five RCTs were of small sample size (100-200 participants) (71,75,76) or underpowered to detect any significant difference in outcome between treatments (46,74). Moreover, the patients included in these studies may not have been representative of patients who receive PETx in the clinical practice in the UK due to the restricted inclusion and exclusion criteria applied in these studies. Except for one study (76), the majority of these studies did not test for ER status, and therefore recruited patients regardless of their ER status. However, as 20% of older women would have ER-negative breast cancer, which will not respond to ETx (30). Therefore, ER negativity may influence the local progression and overall survival rate in the PETx arm and skew the results of meta-analysis in favour toward surgery.

In addition, women recruited to these studies were fit for surgery, and therefore frail women, who are the most likely to be offered PETx in the clinical practice had not been

included (46,71,73-76). These patients have higher risk of postoperative complications or multiple comorbidities that reduce the life expectancy. Excluding those patients may potentially skew the mortality rate in favour of the surgery arm (Table 1.3.). Moreover, all the seven trials included tamoxifen as the PETx and none of these trials considered aromatase inhibitor (AI), which has been shown to be superior to tamoxifen in the adjuvant setting (77).

Although AI may have the potential to achieve better local control in older women with primary breast cancer compared with tamoxifen (Section 1.3.4.2). However, there is currently no RCT data to support this. A large multi-center RCT, 'Endocrine or Surgical therapy for elderly women with mammary cancer' (ESTEem) trial in the UK aimed to assess the efficacy of primary AIs as an alternative for surgery in older people with comorbidity (78) and planned to recruit and randomise 1200 patients aged over 70 years old with primary ER-positive breast cancer to receive either surgery with an AI (anastrozole) or anastrozole alone (78). Unfortunately, this trial was closed prematurely due to poor recruitment (78,79).

**Table 1.3. Randomised controlled trials conducted in older women with primary breast cancer**

| Studies | Population | Age (years) | ER status | Intervention | Comparator | Median Follow-up | Country |
|---|---|---|---|---|---|---|---|
| Johnston, 2012 (72) | 153 | Over 70 | ER positive | Tamoxifen | Surgery+tamoxifen | 6.5 years | UK |
| Fennesy, 2004 (73) | 455 | Over 70 | ER unselected | Tamoxifen | Surgery+tamoxifen | 12.7 years | UK |
| Mustacchi, 2003 (74) | 474 | Over 70 | ER unselected | Tamoxifen | Surgery+tamoxifen | 6.6 years | Italy |
| Gazette,1994 (71) | 200 | Over 70 | ER unselected | Tamoxifen | Surgery | 6 years | UK |
| Fentiman, 2003 (46) | 164 | Over 70 | ER unselected | Tamoxifen | Surgery | 10 years | UK |
| Chakrabarti, 2011 (50) | 131 | Over 70 | ER unselected | Tamoxifen | Surgery | 20 years* | UK |

**(Note)** ER: oestrogen receptor
*Maximum follow-up

### 1.3.3. Primary radiotherapy in older women

Primary RTx could be an option for those patients with ER-negative disease or those who have ER-positive disease but whose cancer has progressed after PETx and unable to receive surgery (80). However, there are limited evidence about using primary RTx in older women with primary breast cancer.

A review conducted by Tang *et al*. (2010) (44) summarised the results of three retrospective cohort studies conducted in France, which assessed the effectiveness of primary RTx in older women over 70 years old (31,81,82). Overall, these three studies enrolled 115 to 396 patient participants, with a median follow-up duration ranging from 3.5 years to 8 years.

Except for one study (31), two small-scale retrospective studies evaluated the use of hypofractionated primary RTx along with PETx for older patients who were aged over 70 years and were unfit for surgery (81,82). One study with a 7-year median follow-up found that 7% of patients who had comorbidities, refused surgery, or had an inoperable tumour were treated exclusively with hypofractionated RTx (82); in this study, the hypofractionated RTx resulted in 96.4% the breast cancer cause-specific survival, 92.4% metastasis-free survival, and 95.8% local regional control rate (82). Another study observed 115 patients who were very old, with comorbidities, or refused surgery and were treated once weekly for 5 weeks with hypofractionated primary RTx (81); the 5-year overall survival was 71% (81).

These two retrospective studies suggested that hypofractionated RTx controls breast cancer progression and could be a good alternative for older women who are unfit for surgery (81,82). Although a large-scale observational study (n=1,755) with median follow-up duration of 8 years, and which described the treatment strategies of older women presented in a single institution in France (including mastectomy, BCTx, and

primary RTx) (31), the results were presented overall for the cohort, including all types of treatments with ten-year local recurrence, and overall mortality rates were 14%, and 49%, respectively (31). Thus, precluded assessing the effectiveness of primary RTx as a sole treatment.

Despite there being direct evidence from RCTs (for PETx) and observational studies (for PETx and primary RTx) specifically conducted in older women, these studies were of small sample size, underpowered to detect any significant difference in outcomes with short follow-up duration, which rendered them inappropriate to inform treatment efficacy in older women with primary breast cancer.

### 1.3.4. Efficacy, effectiveness, and safety of adjuvant therapy

These types of treatment are given postoperatively (i.e. after surgery); thus, this approach is irrelevant to patients who received non-operative therapies.

#### 1.3.4.1. Adjuvant radiotherapy for older women with primary breast cancer

***Efficacy and safety of radiotherapy after breast conservation***

In primary breast cancer, adjuvant RTx is recommended following BCTx regardless of patient age in order to reduce locoregional recurrence (36,83). However, direct evidence from older women with ER (+) showed that patients may not benefit from adjuvant RTx after BCTx, and thus it would be reasonable to omit RTx after BCTx in these groups of patients. Despite there was a direct evidence from older women, older women with ER(+) and smaller primary breast cancer size may not benefit from adjuvant RTx after BCTx, and thus it would be reasonable to omit radiotherapy in these groups of patients.

Two RCTs included 636 (aged over 70 years) (84), and 1326 (aged over 65 years) (85) older women with ER-positive status and had undergone BCTx and received

adjuvant ETx were randomised to receive adjuvant RTx or not. The results showed that patients who received RTx after BCTx had a significantly lower risk of locoregional recurrence compared with BCTx. However, there was no significant difference in overall survival. The primary outcome was locoregional recurrence, and ipsilateral recurrence, respectively, whereas secondary outcome was overall survival. Hence, these studies were 90%, and 80% powered to detect a significant difference in 3 and 5-year locoregional recurrence between the treatment groups, respectively. However, they were not powered to detect a significant difference in overall survival.

Several studies investigated the toxicity of RTx in older people (86-88). These studies found that there is no difference in toxicity between younger and older patients, and thus, differential toxicity would not affect the use of RTx in older patients with primary breast cancer (86-88).

#### 1.3.4.2. Adjuvant endocrine therapy for older women with primary breast cancer

The benefit of adjuvant tamoxifen therapy has been proved in primary breast cancer patients with different ER positivity across different age groups. A systematic review and meta-analysis of 55 RCTs which included 36,689 women with primary breast cancer diagnosed at different ages concluded that a 5-year adjuvant tamoxifen regimen reduced breast cancer recurrence by 47% and the mortality by 26% in a 10-year follow-up period regardless the receptor status (89). Cochrane 2008 has been withdrawn since it was based on earlier cycles of data collection and analysis by the EBCTCG, which were updated in 2001.

Most updated trials investigated the longer-term duration of tamoxifen and showed that continuing tamoxifen to 10 years rather than 5 years produces further reductions in breast cancer recurrence, and overall mortality. Longer Against Shorter (ATLAS) trial, which included 6846 women with early breast cancer and ER-positive status, who were

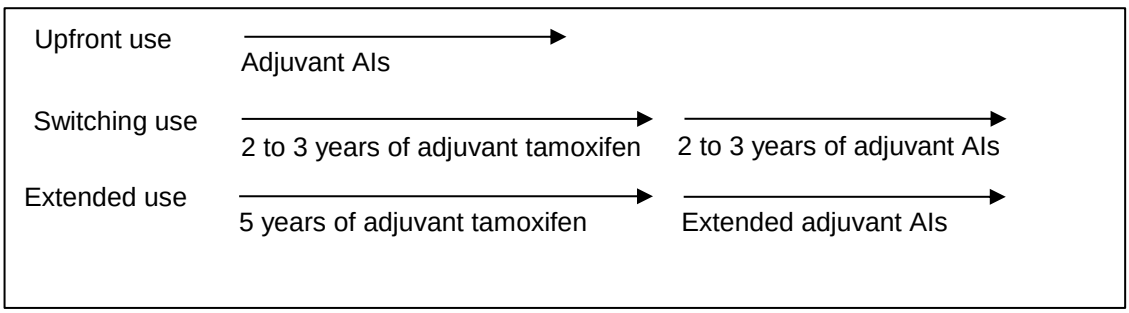
randomised to receive adjuvant tamoxifen for five years (n=3418) or ten years (n=3428) that patients who received adjuvant tamoxifen for ten years have a further reduction in breast cancer recurrence (Rate ratio [RR]: 0.84; 95%CI: 0.76, 0.94; P=0.002) and mortality (RR: 0.83; 95%CI: 0.72, 0.96; P=0.01) as compared to patients who received adjuvant tamoxifen for five years (90).

The effect of the extended use of letrozole for an additional 5 years has also been investigated in the MA-17 trial. This trial included 1918 postmenopausal women (median age: 65 years old) with primary breast cancer and ER-positive status, which were randomly assigned to receive letrozole (959 patients) or placebo (959 patients) for another five years. The results showed that the extended use of letrozole resulted in a further reduction in breast cancer recurrence (HR: 0.66; P=0.01) and non-significant reduction in overall mortality (HR: 0.97; P=0.83) (91).

However, the oestrogenic agonist effect of tamoxifen is detrimental to the endometrium and it increases the risk of endometrial hyperplasia (38) and other menopausal side effects, such as hot flushes and vaginal dryness (38).

Three AI strategies have been proposed for treating postmenopausal women with primary breast cancer, namely up front, switching, or extended use of AIs (Figure 1.1.).

**Figure 1.1. Different strategies for using aromatase inhibitors as an adjuvant therapy in postmenopausal women with primary breast cancer**



The first approach involved prescribing a 5-year adjuvant anastrozole instead of tamoxifen. (77,92). The second approach involved administering two to three years of adjuvant tamoxifen followed by another two to three years of AIs (93). The third approach involved extending the use of AIs after 5 years of tamoxifen (91,94-96).

Josefsson *et al.* (2010) reported a meta-analysis of nine randomised controlled trials that included 28,632 postmenopausal women (median age ranged from 60-68 years) to assess the three different strategies of AIs as an alternative to tamoxifen. Patients who received the upfront (HR: 0.89; 95%CI: 0.83, 0.96; P=0.002) and switching therapy (HR: 0.72; 95%CI: 0.63, 0.83; P<0.00001) had a significantly higher disease-free survival rate than those who received tamoxifen, but no significant difference in overall survival comparing upfront (HR: 0.94; 95%CI: 0.82, 1.08, P=0.39) or extended AIs (HR: 0.86; 95%CI: 0.79, 1.16; P=0.67) against tamoxifen. However, overall survival was significantly higher for patients who switched from tamoxifen to AI therapy than for patients who received tamoxifen (HR: 0.78; 95%CI: 0.68, 0.91; P=0.001) (97).

Josefsson *et al.* (2010) also found that the relative risk (RR) of fracture was significantly higher in the upfront (RR: 1.43; 95%CI: 1.26, 1.62; P<0.0001) and switching (RR: 1.36; 95%CI: 1.05, 1.76; P=0.02) groups comparing against the tamoxifen group, but no significant difference between the extended (RR: 1.17; 95%CI: 0.94, 1.46; P=0.15) and tamoxifen group. Comparing with the tamoxifen group, there was a significantly higher risk of endometrial cancer in the upfront group (RR: 0.34; 95%CI: 0.16, 0.71; P=0.005) but no significant difference in the extended group (RR: 0.45; 95%CI: 0.15, 1.37; P=0.16) (97).

However, none of these nine trials specifically included older women, and hence, it is unclear whether the results can be applied to older women in clinical practice who are more likely to have multiple comorbidities and hence potentially susceptible to more

side effects. Moreover, there is a lack of studies that reported the adverse effects of ETx in older women with primary breast cancer.

#### 1.3.4.3. Adjuvant chemotherapy for older women with primary breast cancer

Adjuvant CTx is given in cycles from 2 to 3 weeks with each cycle followed by a recovery period, and the total CTx duration lasts from 3 to 6 months (38). The use of CTx in older patients is a controversial issue due to their toxicity. Patients with ER-negative breast cancer and patients with triple-negative cancer (no ER, PR, and HER2 in tumour cells) may potentially benefit from adjuvant CTx (42).

The efficacy of adjuvant CTx in treating breast cancer varies by age. A systematic review and meta-analysis included 194 RCTs to assess the use of various surgical treatments with or without adjuvant CTx. The results showed that combination of adjuvant CTx reduced the annual breast cancer death rate in a variety of age ranks, including 40-49 (13%), 50-59 (15%), 60-69 (9%), and 70 (13%) years old. However, only a few women (5%) aged over 70 years were included in these RCTs (98). In addition, the meta-analysis showed that patients with ER-negative tumours derived greater benefits when compared to their ER-positive counterparts, with 27% reduction in the annual breast cancer death rate in patients with ER-positive tumours compared with 30% in patients with ER-negative tumours.

Two observational studies on older women aged over 65 years based on the Surveillance, Epidemiology and End Results (SEER) cancer registries in the USA (99,100), with the latter study including only ER-negative patients, showed that patients with ER-negative breast cancer gained the most benefits from CTx compared with those who did not receive CTx (HR: 0.72; 95%CI: 0.54, 0.96) (99).

A large-scale RCT 'Adjuvant Cytotoxic Chemotherapy in Older Women' (ACTION) assessed the efficacy of using adjuvant CTx in older women aged over 70 years with ER-negative breast cancer, by comparing treatments with and without CTx. Unfortunately, this trial closed prematurely due to poor recruitment (78). The early closure of this trial demonstrated the challenges in recruiting older patients for conducting clinical trials (78,79).

Only few women over 70 years were included in breast cancer trials that received adjuvant CTx due to concerns about the toxicity and safety profile of the CTx (101). CTx-related toxicity is likely to increase with age (102). A retrospective review of four RCTs including 6,487 women with primary breast cancer revealed that the incidence of CTx-related toxicity-associated mortality for women aged <50 years, 51-64 years, and >65 years was 0.2%, 0.7%, and 1.5%, respectively (102). Since older people are generally considered to have multiple comorbidities, they are thus thought to be less likely to tolerate CTx (103,104). Previous studies showed that CTx was less frequently used in older women with higher comorbidities (103,104), the reason being that comorbidities may increase the susceptibility of older patients to the toxicities of CTx (105).

#### 1.3.4.4. Adjuvant biological therapy for older women with primary breast cancer

Trastuzumab is a type of BTx given at 3-week intervals for 1 year, and is used as an adjuvant therapy with or after CTx for patients with HER2-positive early breast cancer (38,42,43).

A meta-analysis of five RCTs compared the use of trastuzumab in combination with CTx against using CTx alone. Three of these five trials recruited older women (16% of the sample size) (106), including the Herceptin Adjuvant Trial (HERA) (107), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 (108), and North Central

Cancer Treatment Group (NCCTG) N9831 (108). However, subgroup analysis was available only from the HERA trial, which showed the benefit of trastuzumab decreased with increasing age; the reduction in annual recurrence rate of breast cancer in older women with over 65 years was only 30% compared with 53% in women of less than 35 years old (107). This may be partly attributed to the diminishing effect of adjuvant CTx benefit with increasing age, which is used in combination with trastuzumb (98).

Cardiac toxicities such as congestive heart failure are the most common side effects of trastuzumab, and hence cardiac function must be assessed before starting the treatment and every 3 months. Moreover, it should be avoided in patients with left ventricular ejection fraction <50% (36).

### 1.3.5. No treatment option for older women with primary breast cancer

In some circumstances, older people may not receive any treatment for their breast cancer. For example, older people with negative ER who refuse surgery and have a contraindication to RTx. In this case, having no treatment is the only option for them (44).

Currently, there is no large RCT that compared the use of different treatment strategies in older women with primary breast cancer. Although, there are large-scale RCTs assessing the efficacy of different treatment strategies in younger breast cancer patients, results of those trials are not applicable to older patients because most participants in those trials were aged less than 70 years, and the strategies only included surgery as the initial treatment instead of other strategies. (44).

### 1.3.6. Subsequent lines of treatments

Subsequent lines of treatments, including second, third, and fourth lines of treatments are offered to patients who experienced a failure on the previous line of treatment by

developing locoregional or metastatic recurrence, or adverse events (109). There is no guideline, particularly for treating older women with primary breast cancer. Although there are several UK national audits looked for the initial breast cancer treatment in older women, they did not observe the subsequent lines of treatments (110,111). Based on The British Association of Surgical Oncology (BASO) and ESMO guidelines for treating recurrent breast cancer reported that the type of subsequent treatments depends on the previous lines of treatments (109,112). For locoregional recurrence, treatment with a curative intent (i.e. surgery) is recommended unless the patients unable to receive surgical treatment and thus systematic treatments such as PETx can be given. In patients who were previously treated by BCTx, a mastectomy should be carried out. In patients who were treated with mastectomy, re-excision in addition to radiation to chest wall and regional lymph node areas is recommended. In those previously irradiated, re-irradiation should be given (109,113).

Metastasis is incurable and hence the main treatment goal is to improve quality of life and prolong survival (109,112). Systematic treatments for metastatic breast cancer are ETx, CTx, bone-directed agents (i.e. bisphosphonates, denosumab) and biological agents (i.e. trastuzumab and lapatinib). The choice of treatments should be made after consideration of factors, such as tumour biology, site of tumour, and previous lines of treatments (109,112). Systematic ETx is given for patients with ER-positive tumour. CTx is indicated for patients with ER-negative tumour, or if endocrine treatment has failed to produce a response. Trastuzumab is given for patients with HER2-positive tumour. Bone-directed agents are given for patients with bone metastasis (109,112,113).

## 1.4. Challenges in treating primary breast cancer in older women and selection of treatment

There is a lack of large RCTs for treating older women with primary breast cancer. Since older people have different biological characteristics, comorbidities, and preferences from their younger counterparts, this may lead to different treatment responses and decisions for the older group as compared to their younger counterparts (44).

### 1.4.1. Tumour biology

ER expression predicts response to ETx (24). In addition, the strength of ER positivity is considered to be one of the predictor factors for the response to ETx (32). The predictive value of ER expression was confirmed by the Early Breast Cancer Trialists' Collaborative Group meta-analysis of randomized trials of 5-year adjuvant treatment with tamoxifen (114). In ER-positive disease, adjuvant tamoxifen significantly reduced the risk of recurrence (HR: 0.61; 95%CI: 0.57, 0.65) and overall mortality (HR: 0.70; 95%CI: 0.64, 0.75) over a 15-year follow-up period, irrespective of PR status and age, nodal status, while tamoxifen had no effect on recurrence or mortality in ER-negative disease (114).

Expression of HER2 predicts the response to biological agents in the adjuvant setting (24). The efficacy of trastuzumab in reducing the risk of breast cancer recurrence has been proved in several large RCTs (107).

As patients get older, the levels of oestrogen and progesterone positive receptors increase, and HER2 positive receptor decrease, and thus, they are more likely to respond to ETx as compared to their younger counterparts (44).

### 1.4.2. Frailty

Frailty is a commonly used term to reflect the state of decline in the physiological reserve of body organs that results in increased vulnerability to any external stressor such as hospitalisation and medical procedures and also leads to dependency on others in daily activities (115,116). Prevalence of frailty increasing with age, older patients who are frail patients are more likely to have complications after receiving surgery, and thus may benefit more from less aggressive therapy, including PETx.

One of the classifications used to stratify the level of patients' fitness was developed by Balducci and Stanta (2000) (105), which defined 'fit' patients as those who were functionally independent without comorbidities, while 'frail' patients were defined as functionally dependent, and/or having three or more comorbidities, and/or one or more geriatric syndromes (105). Patients with intermediate characteristics were defined as vulnerable. This classification approach recommends standard cancer therapy for fit patients, adjusted therapy for those classified as vulnerable, and palliative treatment for those classified as frail (105).

Frailty is correlated with advanced age, being female, and comorbidities (117,118). A prospective analysis of a large cohort of 1,671 older Canadian women aged over 65 years showed that the prevalence of frailty increased by 3% per year with prevalence of 7.5%, 30%, 45%, and 100% in older women of age groups between 65-75, 75-85, 85-95, and over 95 years, respectively (119,120).

Frailty may impact the types of treatment that the older patient may receive (44). Frailty is particularly an issue when undergoing a surgical procedure, because frailty increases the risk of postoperative complications. Two cohort studies, which were conducted on older women aged over 70 (121) and 80 years (122), who had undergone non-cardiac surgeries, showed that frailty was associated with

postoperative complications (such as cardiopulmonary complication, delirium, and gastrointestinal bleeding) (121,122). These postoperative complications were associated with higher 30-day all-cause-mortality rate in women over 80 years old compared with populations younger than 80 years (8% vs. 3%; P<0.001) (122).

These complications that are associated with surgery in older patients who are frail may influence the ability of older patients to receive surgery, and therefore, non-operative therapies might be considered. Several studies showed that PETx can be used in frail older patients who are unwilling to undergo surgery.(58,123,124). Two of these studies were specifically in older patients with primary breast cancer, one of which reviewed the case notes of 104 older women who were treated by PETx in the breast cancer unit at Bedford in the UK between 2001 and 2009 (58), whereas the other study reviewed questionnaires sent to 489 breast cancer surgeons (124). Both studies showed that a large number of the patients received PETx because they were too frail to receive surgery (46%, and 93%, respectively) (58,124).

### 1.4.3. Susceptibility to side effects

With increasing age, there is a decrease in hepatic metabolism of drugs, decrease in plasma protein binding of certain drugs, and a decrease in glomerular filtration rate (105,125). This will lead to an increase in the levels of drugs or their metabolites in the blood plasma and increase in their toxicity, and this will result in an increased response to the drugs and a greater sensitivity to the side effects (105,125). Thus, susceptibility to side effects may lead to drug discontinuation or death. An example of these is the CTx toxicities which increase with age (Section 1.3.4.3).

### 1.4.4. Comorbidities

Several observational studies have shown that the prevalence of comorbidities increases with age (126,127). Comorbidities reflect the presence of other diseases

with the main disease (128). Comorbidities may have an impact on deciding which treatments to choose for older women with breast cancer, based on the number of comorbidities. Older women with comorbidities may be less likely to receive surgery as a primary treatment compared with younger breast cancer patients, and therefore, PETx could be considered as an alternative to surgery.

The Charlson comorbidities index (CCI) is the most common tool used to assess the severity of comorbidities (129). It predicts the one-year mortality for a patient based on their comorbid diseases, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each disease is assigned a score of 1, 2, 3, or 6, depending on the risk of death associated with each one; these scores are summed to provide a total score to predict mortality (129) with higher scores indicating a higher risk of mortality.

The prevalence of comorbidities increases with age; a large retrospective study which included 70,536 primary breast cancer women over 40 years old in the USA showed the proportions of patients who had a CCI score of 0 were 82%, 73%, 61%, and 55%; a score of 1 were 11%, 16.8%, 24.3%, and 27%; a score of 2 were 3.2%, 5.1%, 7.4%, and 9.5% for patients aged 40-49, 50-59, 60-69, and 70-79 years old, respectively (130).

Comorbidities decrease the life expectancy (131). In a retrospective analysis of a large database which included 992 women aged over 70 years old, who had been diagnosed with primary breast cancer between 1971 and 2001, it was found that there was a significant association between baseline comorbidities measured at diagnosis and life expectancy; the life expectancy was 15, 9.6, 5.7, 3.2, 1.6, 1.0, and 0.4 years for 70-year-old patients with primary breast cancer having no comorbidity, one, two, three, four, five and six comorbidities, respectively (131).

Several observational studies have shown that comorbidities were associated with more postoperative complications and death during hospitalisation (130,132).

Dehal *et al*. (2013) showed that patients with more comorbidities were more likely to have postoperative complications such as cardiovascular, renal, or pulmonary complications and were more likely to die during hospitalisation: CCI scores of 1, 2, and ≥3 increased the risk of postoperative complications by 1.7-fold, 2.6-fold, and 4.6-fold, respectively, and the risk of in-patient death by 3.1-fold, 5.4-fold, and 15.8-fold ($P<0.001$) as compared to a CCI score of zero (130). Another study which was based on a national cancer registry in the Netherlands and involved 3,179 breast cancer patients over 65 years old also showed that comorbidities increased the risk of postoperative complications (132). Therefore, the presence of comorbidities should be considered when deciding treatments for patients, since some treatments may have complications that impact on a patient's quality of life without providing any survival advantages to the patient with comorbidities (44).

### 1.4.5. Patients' choices and treatment selection

Patients' choices for their treatment of breast cancer have been shown to change with age (133,134). Though multiple studies showed that patient preference was one of the reasons why older women receive PETx instead of surgery (58,124,135), those patients' preferences may be a reflection of their physician's preference and recommendations (133,134). Therefore, older women's preference towards treatments will be more influenced by their physicians' recommendation compared with younger women (133,134).

## 1.5. National practice in treating patients with primary breast cancer treatments

***Overview of percentage use of PETx***

There is a lack of guidelines related to the use of PETx as an initial treatment in older women with primary breast cancer (36). However, several national audits of UK practice have confirmed the widespread use of PETx in older women with primary breast cancer (111,136). An audit based on a single UK Regional Cancer Network (North Trent) which included 378 patients with invasive or non-invasive breast cancer between March 2002 and August 2002, of which, 210 aged between 55–69 years, and 167 aged over 70 years was conducted to examine the types of primary and adjuvant treatments and assessed the adherence to national guidelines (111). This audit showed that 37% of older women with primary breast cancer over 70 years old were treated with PETx (111). Another audit, based on patients who were newly-diagnosed with symptomatic primary breast cancers obtained from the UK cancer registries as part of breast cancer clinical outcome measure (BCCOM) project, showed that 37.1% of those patients who aged over 80 years old received PETx (136). Since evidence exists for disease control of 2–3 years with primary endocrine therapy, European Society of Breast Cancer Specialists (EUSOMA) and International Society of the Geriatric Oncology (SIOG) multidisciplinary task force recommended to offer PETx for older patients with ER-positive tumours and a short estimated life expectancy (<2-3 years), who were considered unfit for surgery, or refusing surgery (45). A national survey study in the UK demonstrated that the use of PETx remains widespread in the UK, with 93% of 228 UK surgeons are using it for patients with primary breast cancer who were unfit for surgery (124).

***Percentages of using of different treatments across different age groups in national practice, including surgery, radiotherapy, chemotherapy, and endocrine therapy.***

Older women with primary breast cancer were less likely to receive surgical treatment, adjuvant RTx and CTx as compared to younger population in the clinical practice. In the BCCOM project, the proportions of patients receiving mastectomy and BCTx decreased with age from 65% and 73% in women aged less 70 years old to 34% and 26% in women aged more than 70 years old, respectively (110). Moreover, the BCCOM audit revealed that 60% of the patients aged between 70-79 years old received adjuvant RTx compared with 30.6% of patients aged over 80 years old, whereas 12% of positive-lymph node patients older than 70 years old received adjuvant CTx as compared to patients younger than 70 years old (68%). In the North Trent audit, adjuvant RTx was given for 80% and 37% of older women over 70 years old following receiving BCTx, or mastectomy, respectively, whereas adjuvant CTx was given for 0.5% of older women aged over 70 years old (111). In addition, the public health England report, which was based on cancer registry data, National Office Statistics linked with Hospital Episode Statistics (ONS-HES) data, BCCOM project, and NHS breast screening programme (NHSBSP), that were linked together using the NHS organisation number, and included 49,452 patients diagnosed with breast cancer in 2006 (majorities were from England). This report showed that patients aged over 70 years were less likely to received adjuvant RTx (53%) and CTx (16%) as compared to the patients aged between 50-70 years old (RTx: 69%, CTx: 38%) and patients aged less than 50 years old (RTx: 70%, CTx: 72%), respectively (137).

Older women over 70 with ER positive status are more likely to receive adjuvant ETx in the clinical practice with 98% and 82% of older women were given ETx in the North Trent and BCCOM audits, respectively (110,111) whereas 70% of patients aged less than 70 years old received ETx (110).

Over the last few decades, evolving clinical evidence changed the pattern of treatments offered to older women with primary breast cancer in the clinical practice

that prolonged the life expectancy and improved the safety of treatments, including improvements in anaesthetic techniques used in the surgical procedures, introduction of a less invasive type of axillary surgery, AIs and adjuvant therapy following surgery (51,80).

Although the mortality rate for mastectomy under general anaesthesia 20 years ago was approximately 1% in the older women, this has been decreased now due to the improvement in the modern anaesthetic and surgical techniques. The UK National Mastectomy and Reconstruction Audit had demonstrated that overall mortality for breast surgery is less than 0.3% (138). Review of studies which reporting the clinical outcomes of the treatment, specifically in patients over 70 years old reported only two deaths in 615 women undergoing WLE (0.3%), either under local or general anaesthesia (139).

Moreover, for decades the gold standard axillary treatment has been ALND which recently has been replaced by less invasive alternatives, including axillary sampling and SLNB, which were associated with lower morbidity (140) and thus further reduced the risk of surgery. The percentages of patients who received axillary surgery were 92% in the North Trent audit, of which 73% had an axillary clearance, and 27% had a SLNB. The BCCOM audit showed that 74% of the patients who had surgery in England had an axillary surgery.

The survival rates for women with breast cancer have been improved over the last few decades. Five-year relative survival for breast cancer in women has increased from 53% during 1971-1972 to a predicted survival of 87% during 2010-2011 in England and Wales. Thus, this resulted in increasing of life expectancy for older women. However, these patients who are living longer having a higher risk of getting comorbidities and frailty syndrome (141). An analysis of patients over 65 years

admitted to acute provider hospitals in England (January 2005—March 2013) within Hospital Episode Statistics (HES) to examine the prevalence of frailty syndromes over time showed that the coded overall frailty burden, has increased from 12% to 14% between January 2005 and March 2013 (142).

Tamoxifen was introduced as a primary treatment for older women with primary breast cancer in the 1980s (68). However, tamoxifen has largely been replaced by the third-generation aromatase inhibitors as first-line treatment in primary and adjuvant settings (51). There was a trend to use adjuvant treatments, including ETx, RTx, and CTx following the surgical treatment in the recent years. For example, three of the clinical trials included in this Cochrane meta-analysis did not include adjuvant endocrine therapy after surgery. However, since this data was published, women with ER-positive status were considered to receive adjuvant endocrine therapy after surgery in the clinical practice.

## 1.6. Economic evaluation of older women with cancer treatments

### 1.6.1. Increasing pressure of aging population on health care expenditure

Increasing health care expenditure has become a global trend, owing to factors such as aging population, advances in treatment technology (e.g. for cancer treatment), advances in training skills required to deal with the advanced technology, the labour-intensive nature of the health service and rising salaries, defensive medicine, society's increasing expectations, and impact of lifestyle habits on disease epidemiology (143,144). Total health care expenditure in the UK has been increased by 2.7% between 2012 and 2013 with £150.6 billion expenditure from both public and private sectors in 2013 (145); public sector expenditure includes spending by the UK NHS and other government spending, such as health care in prisons and the armed forces while private sector spending includes private households, private medical insurance, and spending by non-profit institutions such as charities (145).

In line with the global trend, aging of populations due to rising life expectancy and/or declining fertility rates has led to an increasing burden on public services, including health and social care.

There is no standard definition for being old (146). Aging is the gradual decline in the functional reserve of the body organs as a result of the passage of time (147) and can be measured chronologically or biologically. Chronological age measures how many years have elapsed since person's birthday whereas biological age measures changes in organ function with time (147), but there is no definitive definition for being old (146). Most developed countries used the chronological age of 60 or 65 years to define older people, which are equivalent to the retirement age in these developed countries (146). However, using the cut-off age of 60 or 65 does not reflect the aging of the physiological organs of the body (105).

Biological age is not necessarily equal to chronological age as the latter does not reflect the decline in organ function (105). Bulducci *et al.* (2000) found that age-related changes such as cognitive impairment, comorbidities, and limitation in functions increases sharply in 90% of people aged over 70 years (105), and Gogan *et al.* (1999) reported that sign of disability (inability to perform the normal daily activities such as washing, walking, etc.) increase in those aged over 85 years old who are referred to as the 'oldest old' (148). These changes with aging will influence treatment effectiveness and should be considered when deciding the optimal treatments for older patients instead of the chronological age (105).

The aging of the population has increased the pressure on the UK NHS to spend more on health care for people over 65 years old, particularly on social care (149,150). The NHS in England has spent around £2.0 billion on people over the age of 65 years old in 2010, and this spending is expected to rise to £2.9 billion in 2022 (150).

### 1.6.2. Arising cancer care burden in aging population

Cancer is one of the top three disease conditions that consume most of the health care expenditure (151). In the UK, the cost of cancer care was £9.5 billion in 2011 (152,153), of which 85% was funded by the NHS (152,153). The most of the UK NHS cancer budget was spent on hospital in-patient costs (excluding surgery; 25%) and followed by the cost of surgery (22%), drug treatments (including costs of drugs preparation and administration) (18%), community services including general practice care (10%), diagnostic procedures (8%), RTx treatment (5%), cancer screening (5%), and palliative care (5%) (152,153).

The cost of cancer care is increasing by 3.7% per year in the UK (152) and is expected to increase to £15.3 billion in 2021 (152,153). The escalating cost of cancer care may be due to the advances in medical technology used in diagnosing and screening cancer, and the development of innovative medicines, thus more patients are diagnosed with cancer. The extra benefits from these developments are generally associated with extra cost, and it has been estimated to increase the total cost spent on cancer by 3.7% per year in the UK (152). In addition, an increasing number of cancer patients will also be identified in the aging population.

Cancer is highly prevalent in older people. With the increase in the number of the aging population over time, the incidence of cancer is expected to increase (4,152,154,155). In England, 292,680 new cancer cases were diagnosed in 2013, of which 49.9% were diagnosed in older people over 70 years (4). There are many cancers, such as prostate cancer, breast cancer, colon cancer, and lung cancer, which their incidences increase with older age (4). In the UK, 318,000 people were diagnosed with cancer in 2010 and this number is expected to increase by 20% in the next 10 years due to the aging population (152). As a result, the demand for cancer care and its associated cost are

expected to escalate. Therefore, economic evaluation is deemed necessary to inform the decision-making (143).

### 1.6.3. Economic burden of breast cancer

Breast cancer has an impact on direct, and indirect costs. While a substantial portion of costs incurred during the first year following diagnosis, breast cancer survivors may require regular inpatient and outpatient care, which have an impact on the long-term costs. In addition, since older women are less likely to receive surgery and thus that would incur lower costs during the initial year following diagnosis as compared to the younger population (156,157). A retrospective cohort study, based on population-based database of the National Cancer Data Repository (NCDR) and Hospital Episode Statistics (HES); including all patients aged over 18 who were diagnosed with colorectal (275,985 patients), breast (359,771), prostate (286,426) and lung cancer (283,940) in England between 2001 and 2010, was conducted to estimate the incidence and prevalence costs of cancer in England and compare costs (i.e. the costs of hospital inpatient and outpatient services provided for all NHS England patients) in patients aged 18–64 and over 65 years old. This study showed that the Incidence costs in the first year of breast cancer diagnosis were higher in patients aged 18–64 (£11,109) as compared to patients aged over 65 (£7,788), however, costs reduced in the years following the diagnosis with patients aged between 18–64 years (£1,316) experienced lower costs as compared with patients aged over 65 years old (£2,277) at ninth year following the diagnosis (156).

Higher incidence costs per patient were incurred by patients diagnosed with higher stage (stage III-IV) breast cancer across all age groups. Stage (I-II) breast cancer was associated with (£10,746) and (£7,597) cost per patient, stage (III-IV) breast cancer was associated with (£13,315) and (£8,804) cost per patient who were aged between 18–64 and over 65 years old in the first year of diagnosis, respectively. These costs

have been reduced in the subsequent years reaching to (£1,279) and (£2,204) in patients with stage (I-II), (£1,848) and (£2,932) in patients with stage (III-IV) aged between 18–64 and over 65 years old in the ninth year following diagnosis, respectively (156).

Patients with stage (I-II) breast cancer aged over 65 years old were less likely to receive surgery within 12 months following their diagnosis (65.97% vs. 80.48%). However, they experienced longer days of hospital stay (6.50 vs. 4.28) and a higher number of emergency admissions (0.34 vs. 0.36), day cases (1.06 vs. 3.72) and outpatient visits (11.18 vs. 16.24) within 12 months of diagnosis as compared to their younger counterparts (156).

Breast cancer imposed higher societal costs as compared to other most common cancers, mainly due to the high economic burden to the UK NHS. A study by Marti *et. al* (2016), based on patient-level data recruited from Leeds hospital, estimated the monthly societal costs incurred by 298 cancer survivors over one year post-diagnosis, of which 136 patients were diagnosed with breast cancer. The monthly societal costs for patients with breast cancer, including the UK NHS (i.e. direct medical cost), patients' out of pocket (direct non-medical costs), and time spent by the family and friends' costs (i.e. indirect cost) were £249.5, £31.0, and £70.8, respectively, whereas the costs to the UK NHS for patients with colorectal, and prostate cancer were £138, and £92, respectively (157).

Indirect costs associated with older women with breast cancer were lower as compared to the younger counterparts because of greater lifetime working productivity. This was based on a sample of breast cancer survivors with median age of 49 years in 2008 in Ireland, who were asked to fill an employment-focused questionnaire (158) that was used later to calculate the costs of the productivity-loss costs, including temporary

disability (i.e. work absence), permanent disability (i.e. reduced working hours), and mortality. Moreover, it showed that age was one of the predictors that are associated with lower productivity costs (actual costs were not available) (158). Productivity costs per person, which were expressed in Euro, were €193,425. Another USA based study, which were used to estimate the productivity loss-cost associated with female breast cancer aged over 18 years old, based on 2008 to 2012 survey data, showed that the annual productivity costs for older women with breast cancer were £3,655 (159).

An aging population and cancer treatments are factors that increase the pressure on health care expenditure. Given the limited resources available to the UK NHS, economic evaluation methods are deemed necessary and helpful in prioritizing which health care interventions should be funded within the limited budget (143). Economic evaluation methods are used to guide decision-making in health care by comparing the costs and outcomes of using different health care interventions from different perspectives (143,160).

Based on the existing knowledge, there is no cost effectiveness study that compares the use of different treatment strategies in older women (161-171) (Chapter 3.), and therefore, conducting this kind of cost effectiveness study is needed.

### 1.6.4. Types of economic evaluation based on the data source

Three approaches are available to conduct an economic evaluation based on the method of data collection, economic evaluation alongside an observational study, economic evaluation alongside RCT, and an economic evaluation based on a decision analytical model (172). RCTs provide a high level of internal validity in terms of intervention efficacy, i.e. good study design that ensures efficient randomisation and subsequently similar distribution of patients' characteristics between different treatment comparators. However, their associated caveats, including short follow-up,

restricted patients' characteristics, failing to present all the comparators in the clinical practice, and failing to present the costs and outcomes actually associated with patients in the clinical practice (protocol-driven costs), limits the generalisability, i.e. the external validity of the RCTs to patients in the clinical practice (160) and a trial may be difficult to conduct due to the previous experience of the failures in conducting large RCTs in older women with primary breast cancer (143). An observational study might play a role in overcoming these limitations, since it represents the actual health gain and resource utilisation that occurred in the clinical practice, and thus enhances the generalisability of results (172). However, some caveats, such as selection bias due to the non-randomisation nature, limit their internal validity (172).

Economic evaluations alongside an observational study or RCT are only applicable if all the key parameters can be obtained from one source, while economic evaluation based on an economic model allows combining data from different resources when model parameters, i.e. transition probabilities, treatment effect, resource use, cost, and utility cannot be obtained from one data source (173); it also enables extrapolation beyond the time horizon of the trial in order to capture all the events and costs associated with different options, especially in chronic diseases (5).

In order to construct an economic modelling, the research question should be identified which includes population, interventions, comparators and outcome measures (143). Evaluation of outcome measures that assess the impact of treatments on older women is needed to inform the design of the economic model. Previous studies reported that since survival benefit from treatments may decrease due to co-morbidities, and sensitivity to side effects with treatments may increase with age, it may be important to consider preservation of quality of life in older women (44,47,101). Therefore, efficacy, and quality of life could be used as outcomes in older women with breast cancer. In addition, It is also necessary to construct an economic model based on

current clinical pathways in the clinical practice (143), and therefore, a description of clinical pathways, which include describing the commonly used treatment strategies and the outcome measures used to assess the efficacy of those treatment strategies are needed.

### 1.6.5. Treatment pathways in older women with primary breast cancer

Clinical pathways describe the commonly used treatment strategies for a cohort of patients, the outcomes such as the efficacy and safety of these treatment strategies and resources associated with them (174). They provide important information about how patients are treated in clinical practice and the costs associated with their treatments (175,176).

RCTs are considered as the gold standard to provide a causal relationship between interventions and outcomes (143). However, the evidence to inform the best treatment strategies for older women with primary breast cancer from these RCTs (Section 1.3.2.2.) may not be generalisable to clinical practice due to the following reasons; patients enrolled in these trials are not representative of patients treated in the clinical practice. In addition to the small sample size, women recruited to these studies were fit for surgery with fewer co-morbidities according to the trials' definition, and therefore frail women, i.e. women with comorbidities and unfit for surgery, who are most likely to be presented in the clinical practice were excluded (46,71,73-76). In addition, these seven trials compared surgery against one alternative treatment strategies, whereas they did not compare all the alternatives that could feasibly be offered to the patients in the clinical practice (46,71,73-76,160). Moreover, patients in the clinical trial are most likely to comply to the prescribed medications and have their regular tests monitored due to the great efforts made by the researchers to ensure that the patients compliant to the trial protocol (160). On the contrary, patients may not receive all extra care or have regular follow up and monitoring test in the clinical practice, therefore their

treatment pathways may be different from the ones described in the trial protocols. Moreover, these RCTs did not report any information about the subsequent lines of treatments and their associated clinical outcomes, and medical resource use associated with the treatment pathways (46,71,73-76,177).

In contrast to the limited generalisability of RCTs, observational studies with longitudinal follow-up have the potential to provide information on the treatment of elderly breast cancer in clinical practice and the long-term consequences (79). However, the observational studies published for older women with primary breast cancer (Section 1.3.2.1.) did not report the treatment pathways, including first and subsequent lines of treatment, and repeated clinical outcomes. Based on the previous systematic reviews of RCTs and observational studies, none of the studies included in these reviews was adequate to solely rely on them to fully describe all the treatment pathways in older women with primary breast cancer.

To provide a reliable estimate of the cost-effectiveness of different treatments used in clinical practice, a detailed estimation of the costs associated with various treatment pathways should be clearly defined, measured, and valued (178). Currently, there is no study reported the treatment pathways of older women in the UK clinical practice. Ideally, a prospective large-scale observational study or clinical audit with large sample size and longitudinal follow-up is preferable to describe all the treatment strategies, and their associated clinical sequences and resource in real life, despite this type of study is time-consuming and expensive (179,180). Alternatively, a retrospective observational study with long-term follow-up using data from pre-existing medical records may be able to describe the treatment pathway of older women and explain how older women are treated in the real life (Chapter 2.).

### 1.6.6. Efficacy, and effectiveness data associated with older women with primary breast cancer

In order to populate the economic model, collection of benefits data (efficacy or effectiveness, and utility data), resource use and cost data is needed (143). Currently, the RCTs available for older women only provided the treatment effect for some health states, either progression to death or recurrence. However, they did not provide the treatment effect for the second progression neither provided patient-level data that can be used to derive time-dependent transition probabilities (181), and thus long-term cohort database, which recorded the subsequent clinical outcomes can provide these transition probabilities (Chapter 4.).

### 1.6.7. Costs associated with treating patients with primary breast cancer

An electronic database search was conducted by using Ovid Medline (1964 to March 2014) and PubMed® (1972 to March 2017) using the following search terms (exp *Breast Neoplasms/ec [Economics], Health Care Costs/ "Cost of Illness"/). The search was limited to English language and humans. In addition, the economic evaluation filter was used in Medline and PubMed databases.

A number of studies have reported costs associated with different aspects of breast cancer care for younger population, ranging from estimating costs, specifically for managing one tumour stage, such as metastasis, to estimate the costs associated with breast cancer pathways starting from breast cancer screening. Richards *et al*. (1993) reported the presented retrospective data on the aggregate cost associated with treating 50 patients with metastatic breast cancer with mean age of 60.5 years (range 32 to 87) based on a retrospective analysis of medical records in the Guy's hospital in London. The mean costs of treatment per patient over 17 months was £7,620 (range: £317, £27,860) (182).

A study by Karnon *et al*. (2005) evaluated the five-year aggregated costs at year 2005 prices associated with treating breast cancer recurrence based on a retrospective analysis of 199 patients with mean age of 59 years who were first diagnosed with early breast cancer in Western General Hospital in Edinburgh between 1991 and 1998 and had experienced recurrence between 1991 and 2004 (183). Another study by Thomas *et al*. (2009) evaluated the direct costs associated with treating breast cancer recurrence in both primary and secondary care, based on year 2005 prices, in a UK population-based study of 77 patients with mean age of 62 years who were identified with relapse between 2000 and 2005 and were followed prospectively for a median average of 3.4 years after having the relapse (184). In a more recent study conducted by Hall *et al.* (2015) (185), the cost of secondary care, based on year 2012 prices, for

patients (mean age: 56 years) diagnosed with breast cancer who remained disease free (DF) between May 2010 to September 2012 was estimated prospectively from case notes identified from Leeds and Calderdale Hospital in the UK.

A study by Remark and Brazil (2004) evaluated the costs of managing metastatic disease based on the 2001 prices using information about resource utilisation collected from a survey of cancer physicians for patients with average survival times of 18 months (186). Wolstenholme *et al*. (1998) presented the mean 4-yearly costs of breast cancer treatment by stage based on a detailed examination of the case notes of 137 breast cancer patients treated in the central England, who were diagnosed in 1991, which were £3,576 for patients with primary breast cancer (187). There was a lack of resource use costs collected for older women with primary breast cancer.

## 1.7. Conclusion

Breast cancer is a highly prevalent cancer and is increasingly diagnosed in older age. The current treatment strategies for older women with primary breast cancer follow guidelines based on evidence from large RCTs that were mainly conducted in a relatively younger population (45). However, the evidence that emerged from these RCTs might not be applicable to older women with primary breast cancer, because these large RCTs tended to enrol a very small percentage (i.e. 9% as in Hutchins *et al.* [1999]) of patients older than 65 years and excluded women older than 70 years (188), and predominantly included surgery as the main initial treatment, which is usually the primary or initial treatment for younger population with primary breast cancer (47).

Moreover, some research has demonstrated that older women with primary breast cancer have different biological factors (higher levels of positive ERs), comorbidities, and patient preferences compared with their younger counterparts, and hence, they

may benefit from other non-surgical treatment strategies such as PETx (28,30,44,189,190). Although PETx has been widely used in the UK with up to 40% of women over 70 years being treated only with PETx based on a national audit conducted in 2002 (111) to treat older women with primary breast cancer, there is a lack of high level of evidence to support its efficacy (5,44).

Treating of older women with primary breast cancer is highly demanding and thus economic evaluation studies are required to treat this group of patients within the limited budget the UK NHS has. However, currently, there is no cost-effectiveness study that compares the use of different initial treatment strategies in older women with primary breast cancer (161-171). Since economic evaluation studies, which are based on an economic model have advantages over the ones based on a single clinical trial, in terms of extrapolation and combining data from different sources, an economic model was used to derive the cost-effectiveness ratio for older women with primary breast cancer.

In addition, there is a lack of long-term descriptions of treatment pathways, efficacy, resource use and cost collected alongside published RCTs and observational studies which hinder using them as the source to populate an economic evaluation based on an economic model, and thus real-life data with long-term follow-up may provide the clinical outcome, resource, use and costs necessary to conduct this type of economic evaluation. Thus, this thesis describes a Ph.D. research of an economic evaluation based on an economic model aimed to assess the cost-effectiveness of using PETx against surgery in older women with primary breast cancer relying mainly on long-term cohort study and other published sources.

## 1.8. Aim of the study

### 1.8.1. Research question

To inform an appropriate clinical decision making treatment, it is crucial to investigate the cost-effectiveness comparing PETx against surgery for older women with primary breast cancer.

The research questions were categorised into four areas:

1. How are older women with primary breast cancer treated in the UK?
2. What are the therapeutic outcomes of different treatment strategies?
3. How much do different treatment strategies cost? What are the key driving factors that influence the cost?
4. What is the cost-effectiveness comparing PETx against surgery? Does the cost offset the benefit?

### 1.8.2. Aim and objectives

This Ph.D. research aimed to investigate the clinical and cost-effectiveness of using PETx against surgery in older women with primary breast cancer. The objectives are

1. To describe the clinical pathways in a cohort of older women with primary breast cancer
2. To evaluate the effectiveness and estimate costs of different treatment strategies
3. To predict long-term cost utility comparing PETx against surgery using a decision analytical model

Four approaches were taken in this Ph.D. research to summarise and synthesise evidence from different data sources. Firstly, a retrospective analysis of a cohort database was conducted to describe the treatment pathways, and evaluate the effectiveness and costs associated with using different treatment strategies (Chapter 2.). Secondly, effectiveness and costs estimated from this chapter provided a vehicle for estimating the cost-effectiveness ratio of PETx against surgery. The limitations of this cohort database, in terms of a short time horizon and a lack of all available information, were addressed and the need for conducting an economic evaluation based on a decision analytical model to combine data from different resources and extrapolate for a lifetime horizon was highlighted.

Therefore, a systematic review of economic evaluation studies was conducted as the third approach to summarise the key methodology of the previously published economic models, to justify and propose an appropriate model for evaluating the long-term cost-effectiveness of PETx against surgery (Chapter 3.). Economic evaluation based on a decision analytical model was carried out as the fourth approach (Chapter 4.) based on the proposed model in the previous chapter; the model was populated using different data sources, including the cohort database and literature. Finally, the main findings from those approaches were linked, presenting the implications of the results to practice and policy makers, and recommendations for future research in this field (Chapter 5.).

Overall, this thesis represents an example of an economic evaluation based on an observational study and economic model. It provides some insight of the importance of conducting this kind of study in older women with primary breast cancer. Moreover, the findings of this Ph.D. research can inform the decision-

maker and health care professional about which treatment strategies are the more cost-effective.

# Chapter 2. Clinical outcomes and costs associated with different treatment pathways for older women with primary breast cancer

## 2.1. Introduction

The advances of treatments in breast cancer disease have extended the survival of breast cancer, and it has become a chronic disease that needs long-term adjuvant therapy to prevent repeatedly recurrent events, thus impacts on long-term treatment effectiveness and resource use. Cost-effectiveness evidence comparing different initial treatment strategies is important to inform the resource-use allocation in older women with primary breast cancer (Chapter 1; section 1.6.). To conduct a cost-effectiveness study, effectiveness, resource use and cost, and utility for different treatment strategies should be collected and later combined to estimate the cost-effectiveness ratio (143).

Currently, none of RCTs and observational studies, which were conducted on older women with primary breast cancer (Chapter 1; section: 1.3.2.2.) reported information about the whole patients' treatment pathways, including subsequent lines of treatments and recurrent events, which are required to fully estimate the medical resource use and costs associated with the patient pathways.

Moreover, there is a lack of studies focused on the total direct costs associated with treating older women with primary breast cancer. There are several costing studies that estimated the resource use and costs for younger population in the UK; these studies were based on single secondary database settings (n=77 to 199) (183,184) or survey of the UK oncologists to estimate hospital or community costs (186). These studies presented costs associated with treating locoregional recurrence, metastatic recurrence, and contralateral tumour. Only one study presented the cost estimates was based on self-reporting of resource use which may be less accurate than cost estimates based on routinely collected resource from primary and secondary care data (186). Five studies were undertaken in a regional hospital trust (182-185,187); of which

three of them were considered generalisable to the UK clinical practice (183-185). However, there is a lack of costing studies that reported disaggregated cost data associated with treatment of older women with primary breast cancer to inform cost-effectiveness models. The previous studies presented aggregated costs data without differentiating between costs for older and younger population and therefore, these studies were unable to provide data on total costs of treatment of older women with primary breast cancer (182-185,187). In addition, these studies only presented costs of one health state (such as metastatic recurrence) (182,186), or aggregated data (i.e. resource use and unit costs were not separated) that cannot be easily converted to inform economic evaluations (183-185).

Since the majority of cancer patients are followed in secondary care settings (i.e. hospital outpatient settings) (191), analysing the hospital-based registry (i.e. a prospective routinely collected dataset that records information on the cancer patients seen in a particular hospital on a regular basis) (179) potentially can provide information about the clinical pathways, effectiveness, resource use, and costs associated with treatment strategies currently available for treating older women with primary breast cancer in the hospital setting. However, there are some issues encounter using these observational studies, including censoring issues and non-randomisation nature of these observational studies (192,193). Imbalance distribution of confounders between the two groups of patients who received different treatment strategies may bias the costs and outcomes, and thus adjusting for these covariates is necessary to provide an unbiased estimate of costs and outcomes for each treatment strategy (192). A number of studies has demonstrated that age, HER2 status, lymph node status, and tumour grade are key drivers of the total costs in patients with breast cancer (183,184). In addition, RCTs on older women with primary breast cancer showed that age, ER status, and treatment allocation are significant predictors of overall survival (46,74).

Censoring issue is common since the clinical trials are followed over a period where some patients do not observe the outcome of interest (i.e. death), and therefore, this will result in incomplete information on outcomes and associated costs for all patients, and would bias the estimate of outcomes and costs if censoring has been ignored (193). Cox-proportional hazard model is the most commonly used regression method to analyse censored time to event data in the medical research (194). This method is widely used in analysing survival to time data in cancer research (195,196), including previously conducted RCTs on older women with primary breast cancer (46,50,71-74).

## 2.2. Aim and objectives

This study aimed to understand the clinical pathways of older women with primary breast cancer and the treatment outcomes and associated costs related to their treatments. The objectives include:

1. To summarise the initial treatment strategies received by older women with primary breast cancer
2. To describe patient characteristics and factors associated with different initial treatment strategies
3. To identify outcomes and consequences related to the different initial treatment strategies
4. To summarise resource use and associated cost estimates with different initial treatment strategies
5. To compare the difference in the outcomes and total direct costs between different initial treatment strategies

## 2.3. Methods

### 2.3.1. Study design and data source

This retrospective cohort study used a longitudinal database of 1,759 older women, who were diagnosed with primary breast cancer at age over 70 years old and treated in a dedicated Primary Breast Cancer Clinic for Older Women from 1973 to August 2010 at Nottingham City Hospital in England.

The database was established as part of a research programme on older women with primary breast cancer. Variables related to individual patients' characteristics, (i.e. age and follow-up), tumour characteristics, (i.e. tumour size, ER status), types of treatment, type of treatment outcomes (i.e. locoregional progression, metastasis, and death) (80) were recorded from 1973 to 2010.

Tumour characteristics were recorded as categorical data. Death and metastatic statuses were recorded as binary data, i.e. whether the event happened or not (80) (Appendix 1.). Furthermore, some additional clinical outcome variables were recorded based on the different types of initial and subsequent lines of treatments that patients received. For patients who received surgical treatment, their disease progression, including local recurrence and regional recurrences were recorded as binary data, i.e. whether or not the patients experienced a recurrence (either local or regional). For patients who received non-surgical treatments, the progression status, i.e. whether the patients experienced a progression (i.e. local and regional), a change in therapy due to the treatments' adverse event, or remained progression free (80) were recorded as categorical data.

Moreover, this database includes information about the initial and subsequent lines of treatment strategies, long-term clinical outcomes over time, and resource use

associated with these outcomes, which is suitable to describe the clinical pathway of older women with breast cancer in the hospital setting.

### 2.3.2. Study cohort

All older women with ER-positive primary breast cancer who received either surgery or PETx as initial treatment and were enrolled in the database in the recent decade (i.e. 2000s onwards), with follow-up duration recorded (i.e. their follow-up duration was not recorded as zero), and did not receive trial medicines were included in this study. In the database, there was no further follow-up or survival data recorded for patients who were discharged back to the general practitioner (GP) practice after receiving their initial treatments, and hence they were not included from this study since there were no data available for them. In addition, patients who received trial endocrine agents, or other medications prescribed only as part of the clinical trials, such as onapristone, gifitinab, or gamma-linolenic acid, were also not included, as these treatments were not prescribed in routine clinical practice. The study cohort was followed from the date of breast cancer diagnosis (recorded in the dataset) to death or the end of the study period (August 2010).

### 2.3.3. Outcome measures

Outcomes measured from the cohort database included clinical outcomes, treatment pathways, patients' characteristics, and health care resources.

#### 2.3.3.1. Clinical outcomes

The primary clinical outcome recorded in this study was death, including breast cancer and overall death, and the secondary clinical outcomes included breast cancer progression (i.e. local-regional or metastatic progression)

Patients' 'survival status' and 'survival time' were identified from the corresponding variables in the database. The progression events for patients who received surgical (i.e. local or regional 'recurrence') or non-surgical treatment strategies (i.e. local or regional 'progression', metastasis) were recorded differently in the database, and those progression events were standardised as locoregional and metastatic progression to enable comparison of outcomes between other initial treatment strategies. The first progression events were identified and included in the analysis.

Since each progression event variable was linked with a time-to-event variable recorded in the dataset, for an individual patient, the event with the shortest time-to-event was defined as the first progression outcome. For example, if the 'time to local recurrence' was found to be shorter than the 'time to metastasis' in patients' records, then the 'local recurrence' would be identified as the first event.

#### 2.3.3.2. Treatment pathways

The initial and subsequent treatment strategies received by individual patients were identified from the variables recorded in the database. Initial treatment was the first treatment that the patients received after they had been diagnosed with primary breast cancer. Any record of the second, third, or fourth line of treatment were identified as subsequent treatments. Adjuvant treatments for patients who received surgical treatment as the first-line treatment were also identified from the database.

The proportions associated with different treatment patterns were presented in a histogram stratified by those who received first, second, or third lines of treatment.

#### 2.3.3.3. Patients' characteristics

Individual patients' age at diagnosis (years), ER status (positive, negative, or unknown), clinical size of the tumour (centimetres), and follow-up duration (months) were identified from the recorded variables in the database.

### 2.3.4. Data management

Since this retrospective database collected for other research purposes, some variables were not recorded. (1) Time to progression on first, second, and third lines on non-surgical treatments (2) Second, third, and fourth-line of treatments. This is a particular issue for economic analysis since the estimation of the total costs requires the estimation of the subsequent treatments, medication prescriptions, and follow-up frequency. Time to progression is important to estimate follow up frequency and non-surgical prescription frequency, whereas second, third, and fourth-lines of treatments are required to estimate the costs associated with those treatments. If one of these data points were missing, the whole costs for the individual pathways will be considered missing.

Omitting the observations with uncompleted total costs (Complete case analysis) during generating the cost-effectiveness ratio will lead to omit the associated effectiveness data, and this, introducing a bias in the effectiveness estimate. Therefore, it is necessary to impute this data, i.e. use some statistical methods to predict the values of these unrecorded observations

Unrecorded variables relevant to the estimation of cost, effectiveness outcomes, and consequently, the CEA were categorised into three categories. Unrecorded variables were related to types of subsequent lines of treatments; and time to progression on initial and subsequent lines of non-surgical treatments (Table 2.1.). Two imputation approaches were used to handle these unrecorded variables, including GLM for

imputing unrecorded time to progression, and multinomial logistic (MNL) regression for the unrecorded treatment strategies.

#### 2.3.4.1. Imputation approach

Regression methods were used to predict other unrecorded data (excluding ER status) of a specific variable in the imputation approach. The choice of the regression method was based on whether the unrecorded variables were categorical or continuous (Figure 2.1.). GLM regression was used to predict continuous variables (197), including time to progression, MNL is commonly used when the dependent variable has more than two categories and it was used to predict the treatment categories and the actual individual treatments in this study (198).

According to existing literature and clinical knowledge, all the covariates which were thought to be associated with the prediction of the data being unrecorded, were identified and included as the independent variables in both MNL and GLM regression models (Table 2.1.) to predict the unrecorded data (as the dependent variables). The predicted means (in GLM) or probabilities (in MNL) were estimated in the regression model by using information only from patients with complete data to substitute the unrecorded data. The imputation approach was used to predict the unrecorded time to progression and types of treatment.

***Variables used to predict unrecorded time to progression following receiving first, second, third and fourth lines of non-surgical treatment***

Only ER status was included as the independent variable in the GLM to predict time to progression after receiving non-surgical treatment as the initial treatment. Previous literature showed ER status and tumour grade to be the predictors for achieving a clinical benefit, i.e. response to treatment within the first six months by reduction in the size of the tumour or remaining stable (199). However, since the tumour grade was

not recorded for all patients, subgroup analysis was conducted for patients whom tumour grade were recorded and thus, tumour grade and ER status were considered as the predictors for the clinical benefit.

The variable - 'Time to progression on prior ETx', i.e. previous ETx for patients who progressed after receiving first, second, third, or fourth non-surgical lines of treatment was also considered as one of the predictors to predict time to progression on second, third, fourth, and fifth lines of treatments, respectively, in addition to ER status (199) (Table 2.1.).

***Variables used to predict second, third, fourth, and fifth-line treatment***

Given the large number of second, third, fourth, and fifth lines of treatment, the types of treatment strategies, i.e. whether it is ETx and non-ETx were predicted first followed by predicting whether it is surgery, ETx, or RTx. After that, the actual individual treatments were predicted within each category; for example, whether the actual individual treatment was mastectomy or wide local excision within the surgical group.

The probabilities of receiving each type of treatment were predicted for each patient based on MNL model. Thereafter, the unrecorded types of treatments were substituted by the types of treatments with the highest predicted probabilities. In order to predict the types of treatment strategies (whether it is ETx or non ETx), patients with recorded types of treatment strategies were first subgrouped based on whether they received ETx as a prior treatment or not, since additional covariate, i.e. 'time to progression on a prior ETx' was used to predict the types of treatment strategies in patients who received a prior ETx. Within the patients who did not receive a prior ETx, literature showed that ER status, type of progression (i.e. the development of metastasis or not), being frail or not, patients' choices were associated with whether the patients received ETx or non-ETx therapy (80,200). However, given that frailty and patient choice were

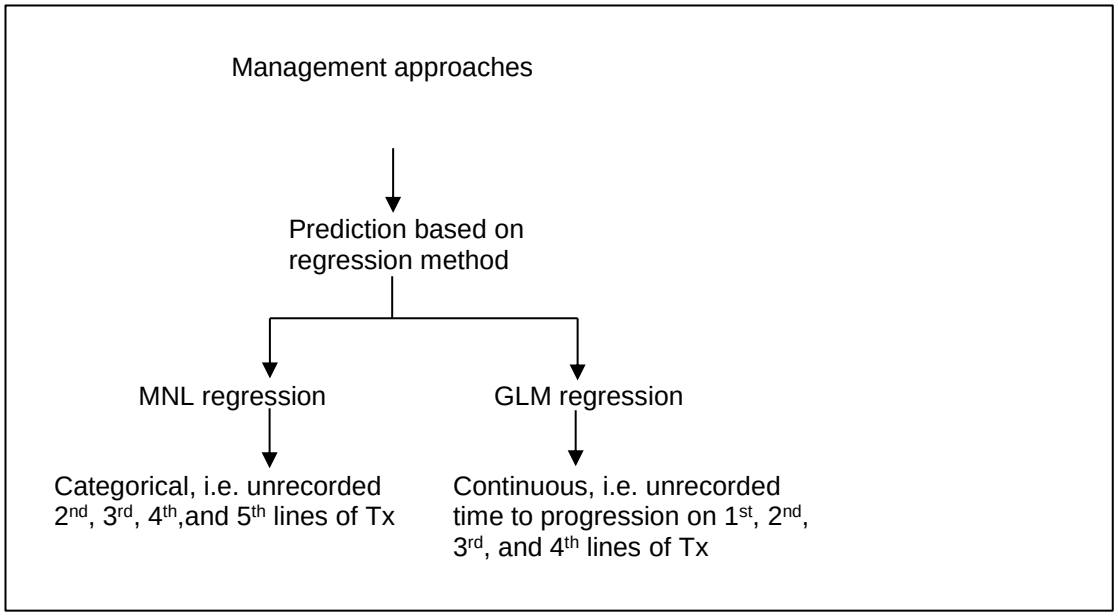
not recorded, ER status, type of progression, and age as a surrogate indicator for frailty were considered as the predictor for treatment selection. Within the patients who received a prior ETx, additional covariates, including 'time to progression on a prior ETx' in addition to the type of progression, age and ER status were considered as the predictors for whether the patients received ETx or non-ETx therapy (Table 2.1.).

Within the patients who were predicted to receive non-ETx therapy, age as a surrogate for frailty, a prior type of recurrence (i.e. the development of metastasis or locoregional), and a prior type of treatment (i.e. surgery, RTx, no treatment [Tx]) were used as predictors for receiving surgery, RTx, or no Tx (80,109) (Table 2.1.).

For predicting the actual individual treatments, literature showed that 'type of recurrence', i.e. whether it is regional or local recurrence, guides the selection of the types of surgical treatment, and hence, was used to predict the types of surgical treatment. Year of commencing the treatment, progression (i.e. whether patients developed metastasis or not), the type of a prior ETx, the type of prior adjuvant endocrine therapies, side effects associated with a prior ETx, and comorbidities have been shown to guide the selection of ETx such as tamoxifen, anastrazole, etc (40,80,201). However, comorbidities and side effects were not recorded, and thus, were not used as predictors for receiving the type of ETx (Table 2.1.).

The median times to progression and proportions of patients who received subsequent lines of treatments were presented for both imputed and complete case analysis.

**Figure 2.1. Strategies for managing the unrecorded variables in the database**




**(Note)** GLM; generalised linear model; Tx: treatment; MNL: multinomial logistic.

**Table 2.1. Covariates used to predict the unrecorded time to progression and subsequent lines of treatment**

| Unrecorded variables | Covariates | Hypothesis |
|---|---|---|
| **Time to progression on first and subsequent lines of non-surgical treatments** | ER status | Patients with ER-positive status have a longer duration of response compared to patients with ER-negative status (199,200) |
| | Time to progression on prior ETx[a] | Patients with longer time to progression on the first-line of non-surgical treatment have a longer time to progression on second-line treatment (199,200) |
| **Subsequent lines of treatment strategies** | | |
| ***Categories of treatment strategies*** | | |
| Predicting ETx, and non-ETx | Age | Older patients were less likely to undergo surgical treatment (using age as surrogate for frailty) (80) |
| | ER status | Patients with ER-positive status respond to ETx, and thus were offered either ETx or surgery, while patients with ER-negative status would not respond to ETx, and thus, were offered surgery or RTx (80) |
| | Development of metastasis or not | Patients with metastasis are commonly treated with ETx treatment, and thus, they are more likely to receive non-surgical treatment compared with patients who did not develop metastasis (80) |
| | Time to progression on prior ETx[b] | Patients who have longer 'time to progression' on the initial treatment were highly likely to benefit from further ETx and thus were put on another ETx. Those who progressed quickly were less likely to benefit from further ETx, and thus, more likely to be treated with a therapy other than PETx (80,200) |
| Predicting type of non-ETx, i.e. surgery, RTx, or no Tx | Age | Patients unfit for surgery were offered either no Tx or RTx. Patients who were fitter (using age as a surrogate) were more likely to have been treated by surgery (80) |
| | Prior type of progression, i.e. the development of metastatic or locoregional recurrence [c] | Patients who developed metastasis are more likely to receive no treatment while patients who developed locoregional recurrence are more likely to receive surgery (80,109) |
| | Prior type of non-surgical treatment, i.e. surgery, RTx, no Tx [c] | For patients who received prior surgery and they developed local or regional recurrence without metastases, the most likely following treatment was surgery (wide excision for local recurrence and axillary clearance for regional recurrence) (109). Since patients who received prior RTx are more likely to be frail with ER-negative receptor, and thus, they were unlikely to receive further active treatment if they developed recurrence. (Based on clinical practice) |

**(Continue Table 2.1.)**

| Unrecorded variables | Covariates | Hypothesis |
|---|---|---|
| **Subsequent lines of treatment strategies** | | |
| ***Actual individual treatments*** | | |
| Predicting the type of surgical treatment | Type of recurrence, i.e. local or regional recurrence | Patients who developed local recurrence are more likely to receive wide local excision, while patients who developed regional recurrence are more likely to receive axillary clearance (80) |
| Predicting the type of ETx treatments | Year of commencing the treatment | AIs were offered to patients since 1995 for patients who have a contraindication to tamoxifen (80). Before the introduction of AIs in 1995, tamoxifen was the first-line therapy for metastatic BC and megacetrol was considered as the second-line treatment for treating primary breast cancer. Since their introduction, AIs replaced tamoxifen as a first-line treatment for metastasis and megacetrol as a second-line treatment for primary breast cancer (40) |
| | Development of metastasis or not | Based on NICE, the choice of subsequent ETx depends on whether the patients experienced metastasis or not. AIs are the most commonly used ETx for treating metastasis while tamoxifen is the most commonly used for treating primary breast cancer (80,109,201) |
| | Prior ETx | The choice of the subsequent line of ETx depends on the previous ETx received as a prior treatment (109,201). For example, if patients received tamoxifen a prior Tx, it will not be offered as a subsequent Tx |
| | Prior adjuvant therapy | The choice of the subsequent line of ETx depends on the previous ETx received in the adjuvant setting (109,201) |

**(Note)** ETx: endocrine therapy; ER: oestrogen receptor; RTx: radiotherapy; CB: clinical benefit; Tx: treatment; AI: Al; ; BC: Breast cancer; NICE: National Institute for Health and Care Excellence
[a]For subsequent lines of treatments and for patients who received ETx as a prior treatment
[b]For patients who received ETx as a prior treatment.
[c]For patients who received non-surgery as a prior treatment.

### 2.3.5. Health care resources use

The patients were treated and followed in the secondary care setting. Data of health care resources incurred in the secondary care setting for study cohort, including different types of treatment and outpatient visits, were collected. Individual patients' treatments included both the first line (including [postsurgical] adjuvant treatments) and subsequent lines (i.e. second, third, fourth, or fifth lines) of treatments. The types of outpatient visits in secondary care included regular follow-up visits, new admission visits, multidisciplinary team (MDT) visits, RTx, and CTx administration visits. (Appendix 2.).

The majority of health care resources utilisation data were identified from the variables recorded in the cohort database, including types of treatment, outpatient visits' duration, duration, and type of ETx. Information that was not available in the database, including types of RTx, types of CTx, frequency, dose, and duration of CTx and RTx, frequency of outpatients' visits and GP visits were estimated based on the researcher's knowledge about clinical practice and advices from the clinician (K.L. Cheung) who was in charge of the data collection. Frequency and dose of ETx were estimated from the British National Formulary (BNF).

The cohort database did not record information on the type of procedure at admission, i.e. whether the procedures were elective (planned admission) or non-elective (unplanned admission), and the average length of stay. An elective admission duration was estimated to be two days based on the average length of stay observed in current clinical practice.

### 2.3.6. Unit cost

A unit cost was assigned to each resource-use item by applying data obtained from different national costing data sources. The unit cost of ETx was estimated from the

British National Formulary 2014 (202). If the unit cost for a medication was not available in the BNF 2014, then a previous version of the BNF was used to derive the unit cost. The unit cost of the medication, including aminogluthamide, was inflated to 2013/2014 UK pound prices based on the Hospital and Community Health Services (HCHS) pay and prices index from the Personal Social Services Research Unit (PSSRU) (203). For example, the inflated unit cost of aminogluthamide was calculated by multiplying the actual unit costs derived from the 2005 BNF by the ratio of the price indexes of 2014 and 2005 (203).

Unit costs for outpatient follow-up, admission visits, and MDT visits were derived from the average unit costs reported in the England NHS reference costs (2013/2014) of the breast cancer medical specialty of outpatient visits (204) (Appendix 4., Appendix 5.). The unit costs of inpatient surgery, RTx (including costs for planning and delivery costs), and CTx (including costs for planning and delivery), diagnostic images, such as computerised tomography (CT) scan were derived from the NHS reference costs 2013/2014 using the relevant Healthcare Resource Group (HRG) codes (204).

The England NHS reference costs attach an average unit cost to a unit health care resource based on their HRG code. These average unit costs included overhead, medical staffing time (i.e. nursing, pharmacy and consultant time resources, blood tests, mammograms, and biopsy procedures) (204). HRG codes are codes for a group of similar patients' events, i.e. treatments in the NHS that consume a similar amount of resources (204).

HRG-4 codes for the inpatient surgical procedures were derived using the NHS healthcare resource grouper (NHS HRG-4 grouper, 2013/2014) software (205), which combines operating procedure code supplements (OPCS-4) and the 10th revision of the International Statistical Classification of Diseases (ICD-10) codes to generate the

most relevant HRG-4 code based on the patients' length of stay, main specialty, number of episodes and spells, age, sex (205). The ICD-10 and OPCS-4 codes have been chosen based on discussion with a clinician (K.L. Cheung) (Appendix 2., Appendix 3.)

The choice of the NHS average unit cost for each surgical procedure was based on these generated HRG-4 codes (Appendix 4.).

Regarding the axillary surgery, based on the costing report for the NICE guideline, additional costs were not considered for the preoperative assessment of the axilla, including mammogram and guided needle sampling since they were included in the surgical costs. SLNB and axillary clearance, which were conducted based on preoperative assessment, were considered within the same episode since they were carried out within the same surgical procedure, whereas axillary clearance conducted following SLNB was considered as a different episode (49).

The average length of stay (LOS) was not recorded in the database, and therefore assumptions were made to estimate the average length of stay for older women. NICE guideline showed that the median length of stay across England in 2006 was 2 days for patients who received BCTx whereas a median length of stay of 5 days for mastectomy (age of patients has not been defined) (36). Similarly, study showed that the mean length of stay for patients underwent mastectomy (mean age: 60 years old), and BCTx (mean age: 58 years old) were 5, or 3 days, respectively (206). This study retrospectively analysed the cases of women diagnosed with breast cancer (80% were primary breast cancer) in the Northern & Yorkshire and West Midlands cancer registry regions between 1997 and 2005 to identify the factors predicts the average length of stay and showed that age, comorbidities, axillary clearance were predictors of hospital length of stay after the initial surgical procedure (206). Undergoing BCTx was

associated with 33% shorter stays compared to undergoing mastectomy (LOS: 0.67; 95%CI: 0.66, 0.68). Older age was associated with an increase in 11% (LOS: 1.11; 95%CI: 1.11-1.11) per 10 year increase in age. Presence of comorbidities and undergoing axillary clearance were associated with an increase in 8% each in LOS (LOS: 1.08; 95%CI: 1.07, 1.09) and (LOS: 1.08; 95%CI: 1.07, 1.10), respectively (206).

Therefore, the average length of stay for each patients in this cohort database was estimated based on their age and undergoing of axillary surgery. Due to the high prevalence of comorbidities in older women, all patients were assumed to have comorbidities and consequently the 8% increase were added for all patients. For example if patients aged 70 years old with comorbidities, underwent mastectomy and axillary clearance, the estimated LOS was equal to 5.91 days using the formula 5+(5*0.08)+(5*0.08)+(0.11*(1 refers to 10 year increase in age))= and then were rounded to the higher integral number, i.e. 6 days.

Thereafter the estimated LOS was used in the HRG grouper. If the HRG code generated from the HRG grouper have a shorter average length of stay than the estimated hospital length of stay, the assigned unit costs were adjusted for the episode's LOS using excess bed days' costs provided by the NHS reference costs (207). The adjustment was performed by subtracting the episode's duration from the mean length of stay for that particular type of episode, and then the cost of any excess days was added to the episode's total cost using the following equations (208,209).

NHS reference cost+( excess bed days costs (the average cost for one day* (estimated average LOS – average LOS from NHS reference costs).

The average unit costs for RTx, CTx, outpatients, and diagnostic tests were directly derived from the HRG-4 codes listed in the NHS reference cost.

### 2.3.7. Direct medical cost

Direct medical costs, i.e. the costs of treatment pathways for breast cancer incurred in the secondary care setting were included in the cost analysis. Diagnostic procedures, including the diagnostic images, and needle core biopsy, were not included in the analysis since all patients underwent the same diagnostic procedures before receiving the first-line surgical or non-surgical treatment (36). Moreover, capital costs were not included in this analysis, as it was incurred in advance when the hospital was constructed (143,160).

Direct total medical costs were calculated for each patient during the survival time period. Additional regular follow-up visits and endocrine prescriptions in case of receiving a prior ETx in the form of ETx and PETx were attached for patients who remained alive at the end of the study follow-up period based on their estimated survival time. The total costs were calculated by multiplying the quantity of each resource use item by its unit cost and reported in UK pounds (£) at 2014 prices (Table 2.2.).

**Table 2.2. Unit cost of health care resources categories**

| Health care resources | Number | Cost (£) | Source |
|---|---|---|---|
| Outpatient new attendance for disease progression | 1 | 169 | NHS reference cost 2013/2014 |
| Outpatient follow-up visit | 1 | 119 | NHS reference cost 2013/2014 |
| MDT | 1 | 86 | NHS reference cost 2013/2014 |
| **Surgery based on the generated HRG-code** | **Number** | **Costs (£)** | |
| Unilateral minor breast procedures | 1 | 1201.95 | NHS reference cost 2013/2014 |
| Unilateral major breast procedures with CC score 0-2 | 1 | 2635.78 | NHS reference cost 2013/2014 |
| Unilateral intermediate breast procedures with CC score 0-2 | 1 | 2109.73 | NHS reference cost 2013/2014 |
| Malignant disorders of lymphatic or haematological systems, with CC score 0-2 | 1 | 2481.01 | NHS reference cost 2013/2014 |
| **Endocrine therapy (oral administration)** | **Pack size** | **Costs (£)** | |
| Tamoxifen tablet 20 mg once daily | 30 tab | 2.27 | Feb BNF 2014 |
| Arimidex (anastrozole) tablet 1 mg once daily | 28 tab | 68.56 | Feb BNF 2014 |
| Megacetrol acetate (megace) tablet 160 mg daily | 30 tab | 19.52 | Feb BNF 2014 |
| Fulvestrant (faslodex) tablet 500 mg every two weeks for the first three doses and then every month | 1 tab | 522.41 | Feb BNF 2014 |
| Aminoglutethamide 250 mg tablet once daily | 56 tab | 24.27 | Feb BNF 2005 |
| Aromasine (exemestane) tablet 25 mg once daily | 30 tab | 88.8 | Feb BNF 2014 |
| Letrozole tablet 2.5 mg once daily | 28 tab | 3.32 | Feb BNF 2014 |
| **Radiotherapy** | **Fraction** | **Costs (£)** | |
| Delivery of external beam radiation | 1 | 126 | NHS reference cost 2013/2014 |
| Planning of external beam radiation | Whole RTx | 796.9 | NHS reference cost 2013/2014 |
| **Chemotherapy** | **Cycle** | **Costs (£)** | |
| FEC 75 mg acquisition cost | 1 | 284 | NHS reference cost 2013/2014 |
| FEC 75 mg delivery cost | 1 | 165 | NHS reference cost 2013/2014 |
| FEC 100 mg acquisition cost | 1 | 284 | NHS reference cost 2013/2014 |
| FEC 100 mg delivery cost | 1 | 165 | NHS reference cost 2013/2014 |
| Docetaxel 75 mg acquisition cost | 1 | 576 | NHS reference cost 2013/2014 |
| Docetaxel 75 mg delivery cost | 1 | 165 | NHS reference cost 2013/2014 |
| CT scan | 1 | 129 | NHS reference cost 2013/2014 |

**(Note**) FEC: fluorouracil (5FU), epirubicin, and cyclophosphamide; CC: Charlson comorbidity; HRG: Healthcare Resource Groups; CT: computerised tomography; PSSRU: Personal Social Services Research Unit; BNF: British National Formulary; NHS: National Health Service; RTx: radiation

### 2.3.8. Data analysis

#### 2.3.8.1. Descriptive statistic for the outcome measures

Descriptive Statistics were used to present variables related to characteristics of patients and to compare between PETx and surgery. Normally distributed continuous variables, such as age and clinical size were presented as mean ± standard deviation (SD) and compared for PETx against surgical treatment using an independent t-test. Non-normally distributed continuous variables, such as follow-up duration were presented as a median ± interquartile range (IQR) and compared for each initial non-surgical treatment against surgical treatment using the Mann-Whitney test. Categorical variables, i.e. tumour grade were presented as the proportion of patients within each initial treatment strategy and compared for PETx against surgical treatment using the Chi-square test. Initial, second, and third lines of treatment strategies were presented as the proportion of patients within each line of treatments. A P-value of less than 0.05 demonstrated a statistically significant of initial non-surgical against initial surgical treatments.

The mean costs overall for all patients and for each treatment strategy were presented as an arithmetic mean with CI using the data generated for bootstrapping for both imputed, complete case, and subgroup analyses (210,211). Although cost data is commonly skewed distribution, the arithmetic mean is the most commonly used parameter to summarise the central tendency of the cost data, because health policy makers are interested in the total costs of adopting a new treatment in the whole patient population which can only be obtained by multiplying the arithmetic mean cost by the total number of patients (210,211), and hence bootstrapping approach with replacement was used to achieve the approximate normality of data distribution, which allowed the comparison of arithmetic means using a parametric t-test (212).

Bootstrapping is a database simulation method for evaluating statistical precision that allows comparing arithmetic means while avoids making assumptions about the distribution of observed mean cost data. The bootstrapping process includes selecting random values from the original sample with replacement to produce a bootstrapped sample, then the statistic of interest (mean) was calculated for this new sample. This sampling process was repeated around 10,000 times to create a sample of bootstrapped means with a distribution and then mean cost was calculated for the bootstrap distribution. The 'observed mean costs' of patients who received PETx as an initial treatment were compared to patients who underwent surgery by pairwise parametric t-test, using the data generated from bootstrapping.

The distribution of the 'observed mean costs' during the follow-up period for the individual patients were presented in a histogram.

#### 2.3.8.2. Survival analysis of all-cause and breast cancer mortality

The proportion of breast cancer progression (i.e. locoregional and contralateral, metastatic progression), all-cause and breast cancer mortality over time was presented using the Kaplan-Meier survival curve (213). Cox's proportional hazard model was used to analyse the proportion of breast cancer progression, all-cause and breast cancer death rates over time by adjusting relevant covariates (196). Previous trials conducted on older women with primary breast cancer tested the potential prognostic covariates' impact on the overall or breast cancer survival, and progression (including ER status, clinical size, type of treatment, age, tumour grade, degree of ER positivity, PR status, axillary stage, and age) have shown that ER status, types of treatment treatments, clinical size, and axillary stage (6,31,46,73,74) were associated with the breast cancer progression, and overall and breast cancer survival. In addition, age (74) was associated with overall death. However, since axillary stage was only obtained from the surgical specimen for patients who underwent surgical treatments,

and therefore it was not available for patients who received PETx. In addition, since the included cohort was restricted to the patients with ER-positive status and previous literature showed that there was no significant difference in breast cancer death between patients with H-score over 250 who received surgery and PETx (69), subgroup analysis was conducted by degree of ER positivity and was included as a potential covariate in Cox regression. This study used a stepwise backward elimination method which included all the potential covariates (i.e. age, degree of ER positivity, tumour grade, clinical size, and treatment strategies) in the model and then excluded covariates one at a time from the model, according to which was not statistically significant until all covariates remaining in the model were statistically significant. Results of Cox's regression were presented as a HR for each covariate with 95% confidence interval (95%CI), and a P-value less than 0.05 was considered as statistically significant.

Although the Cox model allows the baseline hazard rate to change overtime, it assumes constant hazard ratio overtime (196), i.e. the hazard or mortality rates are proportional at any point of time across the different levels of categorical variable compared to its reference group (proportional hazard assumption). If the HR for specific variable varies with time, assuming a constant hazard ratio would mislead its HR estimate (214), therefore, the proportional hazard assumption was tested using the 'Schoenfeld residuals test' which estimates the residuals for each covariate (known as Schoenfeld residuals) (215), tests the independence between residual and time and provides test results in P-value.

In the Schoenfeld residuals test, a $P<0.05$ implies that the covariates violate the proportional hazard assumption (195,214,216), i.e. the hazard ratio of each category within each covariate compared to the reference group is changing with time (214), in this case, a time-varying interaction expression was added to the covariates that

violated the proportional hazard assumption to imply the non-proportionality of the hazard ratio.

Therefore, each of these covariates would have two regression coefficients, one for the main effect and another for time varying effect. For the variables with proved time-varying effect, the estimated covariate effect on the mortality rate at a particular time point was obtained using the following formula:

HR = HR (main effect) * HR (time varying effect)$^{(t)}$,

where:

HR (main effect): is the HR for the main covariate effect

HR (time varying effect): is the time varying HR for the covariate

t: is the particular time point

#### 2.3.8.3. Generalized linear model

Generalized linear model (GLM) is a commonly used approach to overcome some of the flaws associated with the non-normally distributed data (193). This model enables modelling the effect of the covariates on the mean total cost on their original scale by offering different distribution families and links to choose from (197). The non-normally distributed costs were analysed by the GLM regression (197) by adjusting relevant covariates (i.e. tumour grade, treatments (31,73,74), and age (74)) selected in a stepwise backward elimination approach. Although HER2 and lymph node status were proven as significant predictors in the literature, they were not included due to their incomplete information and being only recorded for the surgical group, respectively. Some diagnostic tests were used to inform the choice of the appropriate type of distribution and link function (197). Modified park test was used to identify the best fit distribution for the survival time and cost data (197). The most commonly distributions that were tested in the GLM were Gaussian, gamma, Poisson, and inverse Gaussian (193,197).

Modified park tested the null hypothesis that there is no significant difference between distribution of dependent variables (i.e. the cost data) and the distribution that has chosen to fit these data using the Chi-square test (217). A P-value >0.05 implied that the chosen distribution was the most appropriate distribution for the model (217).

Link test was used to identify the best link function between the covariates and the dependent variables, including 'observed mean survival times', and 'mean costs' (218).The link function tests described how the 'observed mean survival times' or costs were related to the covariates included in the GLM (197). Log and identity link functions were tested in the GLM (197). Identity link assumes that each covariate has an additive effect on the total mean survival times or costs. The log link function assumes that each covariate has a multiplicative effect on the dependent variables.

Since the log link function was tested as the appropriate distribution, the exponentiated (anti-logged) coefficient provided an estimate of the ratio of mean which was re-expressed as the percentage increase in mean survival time or cost per unit increase in the covariate (in case of continuous variable) or percentage increase in mean survival time or cost for each categorical variable group as compared to the reference group (in case of categorical variables) (197) .

Results of GLM regression were presented as a mean ratio of costs for each covariate with 95%CI for imputed, complete case and subgroup analyses, and a P-value $>$0.05 was considered as statistically significant.

### 2.3.9. Ethical consideration

The database used in this study was established as a part of an ongoing research programme in older women with primary breast cancer in Nottingham breast Unit was

approved by the Research Ethics Committee at the Nottingham City Hospital under ethical approval number C2020313.

## 2.4. Results

### 2.4.1. Patients' characteristics

Of the 672 patients included in the cohorts, the mean age was (78.85, SD: 6.08) years and the median follow-up duration was 43 (range: 24 to 68) months. Most patients received surgery (n=350; 52.08%) or PETx (n=322; 47.92%) as the initial treatment strategy. Of the 350 patients who underwent surgery as the initial treatment, 469 (54.0%) received adjuvant therapy. The most common adjuvant therapy was ETx (n=164; 46.86%), followed by combination of RTx and ETx (n=88; 25.14%), and RTx (n=37; 10.57%).

The mean age of patients who received PETx (82.66, SD: 5.66) years as the initial treatment strategy were significantly older than patients who received surgical treatment (75.35, SD: 3.99) years as the initial treatment (P<0.0001). Comparing to patients who received surgery as the initial treatment, patients who received PETx as the initial treatment had a significantly larger tumour size (mean: 2.88 vs. 2.07 cm; P<0.001). Furthermore, patients who received surgery as the initial treatment had significantly longer follow-up duration (median: 53; IQR: 34, 75 months) compared with patients received PETx (median: 34; IQR: 16, 58 months) (Table 2.3.). However, there was no significant difference in tumour grade across different tumour grade.

Overall, 519 (77.23%) were remained alive (i.e. censored) during the study period and 153 (22.67%) patients died, of whom 33 (4.91%) died due to breast cancer and 120 (17.80%) died due to other causes, respectively. The causes of death were categorised into breast cancer deaths (breast cancer as the first cause of death on the death certificate) and non-breast cancer deaths (as on the death certificate or for women with unknown causes of death, if they died within 1 year of last follow-up without clinical evidence of metastases). The causes of death were recorded from case

notes, supplemented by information from the general practitioners for those patients who were discharged back to their care, due to patient preference (80).

**Table 2.3. Characteristics of the included older women with primary breast cancer uncontrolled for confounders**

| Characteristics | Total (N=672) | Surgery (Reference) (n=350; 52.08%) | PETx (n=322, 47.92%) | P-value |
|---|---|---|---|---|
| **Mean age ±SD (years)** | 78.85±6.08 | 75.35±3.99 | 82.66±5.66 | <0.001 |
| **Median follow up (months) (Interquartile range)** | 43 (24 to 68) | 53 (34 to 75) | 34 (16 to 58) | <0.001 |
| **Mean of clinical tumour size±SD (cm)** | 2.46±1.31 | 2.07±1.37 | 2.88±1.09 | <0.001 |
| **Tumour grade (n%)** | 502 | 232 | 270 | |
| grade 1 | 127 (25.30%) | 63 (27.16%) | 64 (23.7%) | 0.33 |
| grade 2 | 330 (65.74%) | 145 (62.50%) | 185 (68.52%) | |
| grade 3 | 45 (8.96%) | 24 (10.34%) | 21 (7.78%) | |

**(Note) n: number; ER: oestrogen receptor ; SD: standard deviation; PETx: primary endocrine therapy**

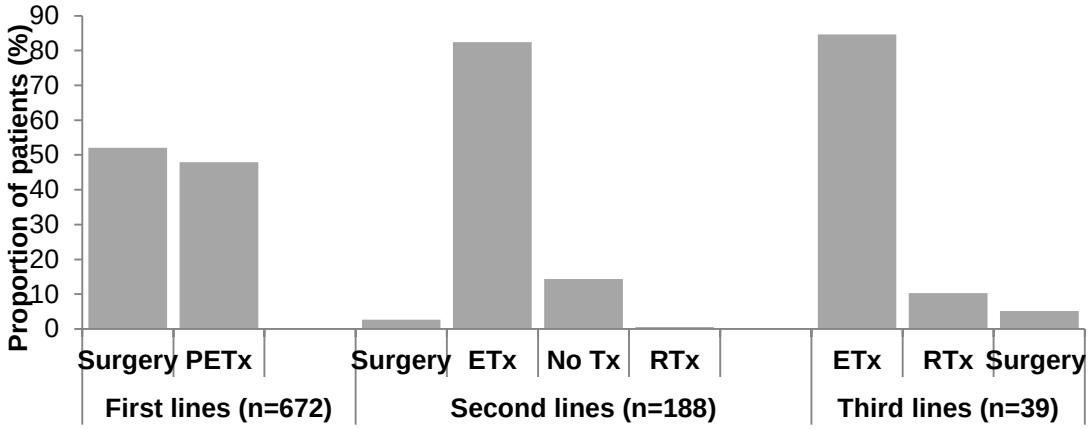
### 2.4.2. Treatment pathway

Of the 672 included patients, 672 (100%) received first-line treatment, 28% (n=188) received second-line treatment, and 5.8% (n=39) received third-line treatment.

Of the patients who received second-line treatment, the majority received ETx (82.45%, n=155), followed by surgery (2.66%, n=5), no Tx (14.34%, n=27), and RTx (0.53%, n=1). Among the patients who received third-line treatment, the most common treatment received was ETx (84.62%, n=33), followed by RTx (10.26%, n=4), and surgery (5.13%, n=2) (

Figure 2.2.).

**Figure 2.2. Proportion of patients who received first, second, and third line treatments**




**(Note)** PETx: primary endocrine therapy; Tx: treatment; ETx: endocrine therapy; RTx: radiotherapy

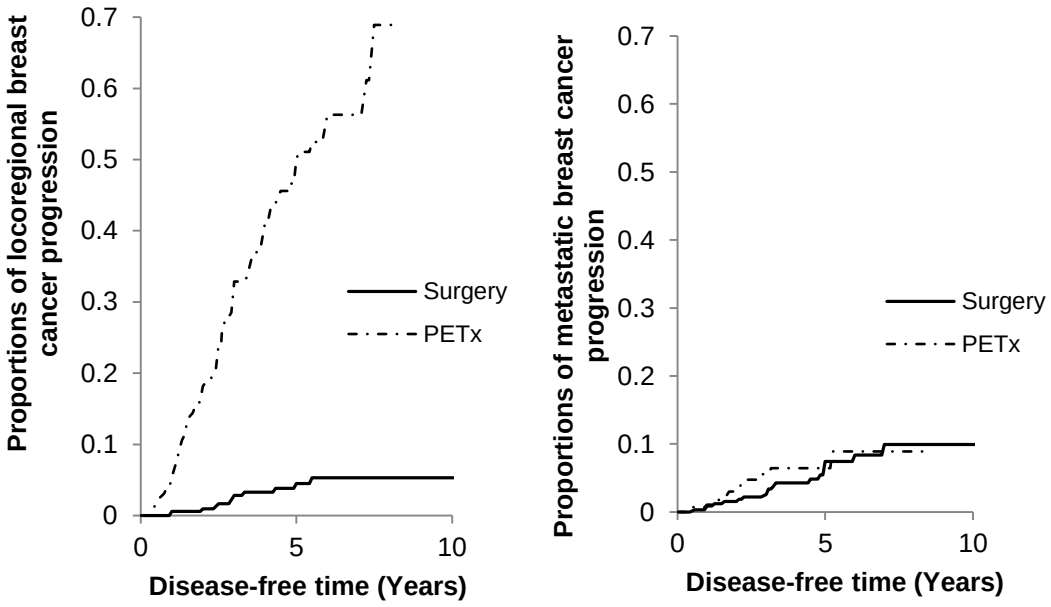
### 2.4.3. Clinical outcome pathway

#### 2.4.3.1. Breast cancer progression

As compared to surgery, the proportion of locoregional and contralateral breast cancer-related mortality was significantly lower for the patients who received PETx treatments (Log rank test P-value<0.001) (Figure 2.5.). The proportion of patients who had developed local disease progression within 5 and 10 years in the surgical group were 4.50% and 5.29%, respectively, whereas 50%, 68% in the PETx group. The median locoregional progression for the PETx arm was 5 years and the median locoregional progression for the surgical arm was not reached.

However, there was no significant difference in metastatic progression between the two groups (Log rank test=0.42). The proportion of patients who had developed metastatic progression within 5 and 10 years in the surgical group were 4.50% and 5.29%, respectively, whereas 6.40%, 8.90% in the PETx group.

**Figure 2.3. Kaplan-Meier survival curve of first breast cancer progression stratified by the initial treatment strategies**



The stepwise backward elimination approach in the Cox proportional hazard model identified that type of initial treatment strategy, clinical size and H-score were significantly associated with the breast cancer-progression rate. In addition, the results of the Schoenfield residual statistical test revealed that proportional hazard assumption hold for those three variables, which implied that the effects of initial treatment strategies, clinical size, and H-score on the progression rate do not vary over time. Therefore, the interaction terms were not included in the model for all these covariates, which implies that covariates' effect on breast cancer progression varies with time (Table 2.5.). Compared with patients who received surgery as the initial treatment, patients who received PETx (HR: 5.87; 95%CI: 3.93, 8.79) had a significantly five times higher risk of breast cancer progression (Table 2.5.).

A significantly higher 26% risk of breast cancer progression was also associated with each one cm increase in clinical tumour size (HR: 1.26; 95%CI: 1.09, 1.46). (Table 2.5.). However, the increase in breast cancer progression with each score increase in H-score (HR: 0.996; 95%CI: 0.993, 0.999) was very small

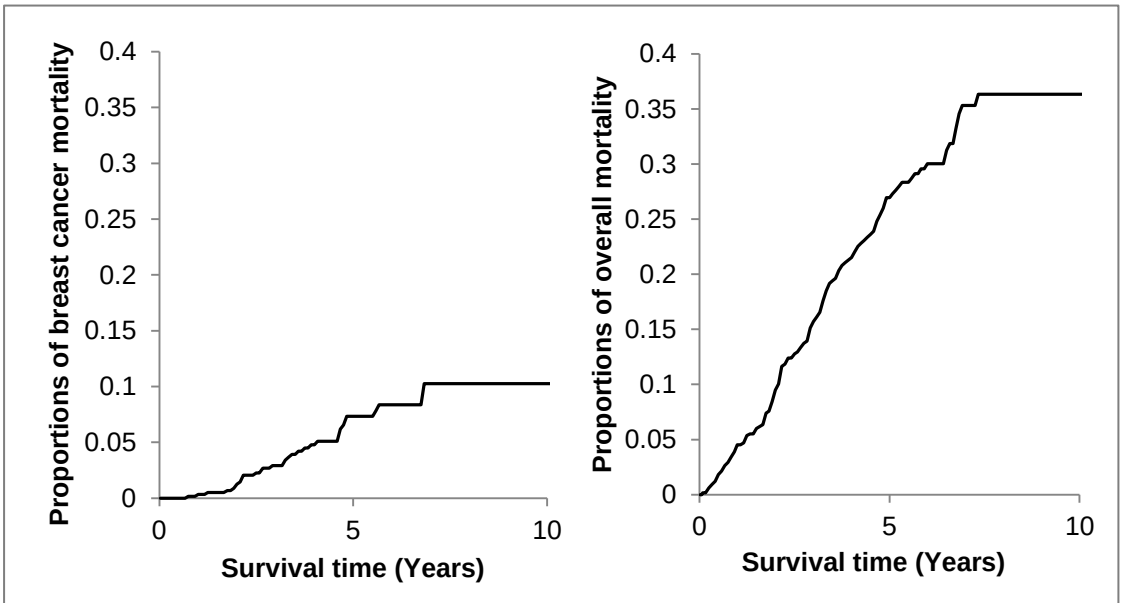
**Table 2.4. Covariates associated with breast cancer progression in the Cox proportional model**

| Covariates | Hazard ratio (95%CI) | P-value |
|---|---|---|
| **Type of treatment strategy** | | |
| Surgery | - (reference) | - (reference) |
| Primary endocrine therapy | 5.88 (3.93, 8.79) | P<0.001 |
| **Clinical size** | 1.26 (1.09, 1.46) | P<0.002 |
| **H-score** | 0.996 (0.993, 0.999) | P=0.01 |

### 2.4.3.2. All-cause mortality and breast cancer mortality

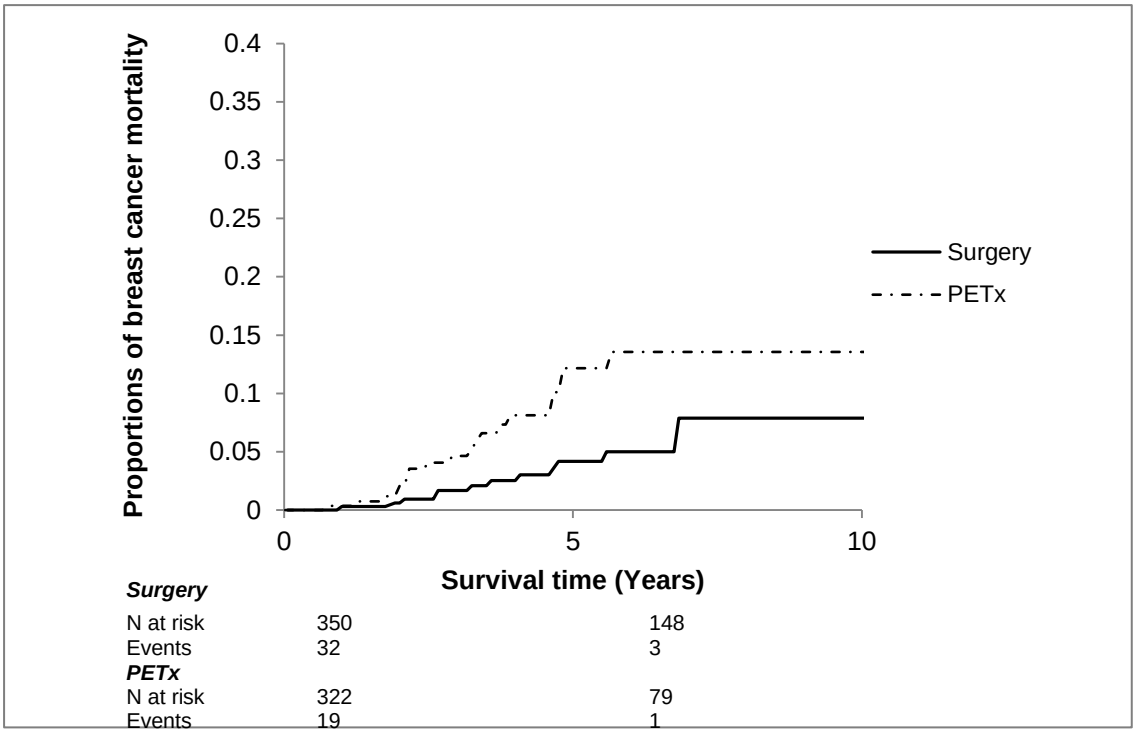
Overall, 153 (22.7%) patients died during the study period, of whom 33 (4.9%) died due to breast cancer and 120 (17.8%) died due to other causes, respectively. The proportions of all-cause mortality at 5 and 10 years after the diagnosis of breast cancer were 26% and 36%, respectively. The proportions of breast cancer-related mortality rates were 7.3% and 10.26% at 5 and 10 survival time years, respectively (Figure 2.4.). As compared to surgery, the proportion of breast cancer-related mortality was significantly lower for the patients who received non-surgical treatments (Log rank test P-value<0.001) (Figure 2.5.). The proportions of breast cancer-related mortality at 5 and 10 survival time years were 4% and 8%, respectively for patients who received surgery, while 12% and 13.5%, respectively, for patients who received PETx. The median overall survival for the PETx arm was 2.9 years and the median overall survival for the surgical arm was not reached. Whereas the breast cancer survival for the surgical and PETx arms.

**Figure 2.4. Kaplan-Meier survival curve of overall mortality and breast cancer mortality**




| N at risk | 762 | 227 | | N at risk | 762 | 227 |
|---|---|---|---|---|---|---|
| Events | 29 | 4 | | Events | 139 | 17 |

**Figure 2.5. Kaplan-Meier survival curve of breast cancer mortality stratified by initial treatment strategies**




**(Note)** N: number of patients; PETx: primary endocrine therapy

### Overall mortality

The stepwise backward elimination approach in the Cox proportional hazard model identified that type of initial treatment strategy, clinical size, H-score, and age were significantly associated with the overall death rate. In addition, the results of the Schoenfield residual statistical test revealed that proportional hazard assumption hold for those three variables, which implied that the effects of initial treatment strategies, clinical size, H-score, and age on the death rate do not vary over time. Therefore, the interaction terms were not included in the model for all these covariates, which implies that covariates' effect on overall mortality varies with time (Table 2.5.).

Compared with patients who received surgery as the initial treatment, patients who received PETx (HR: 2.78; 95%CI: 1.79, 4.33) had a significantly higher risk of all-cause death (Table 2.5.).

A significantly higher 30% risk of all-cause death was also associated with each onecm increase in clinical tumour size (HR: 1.32; 95%CI: 1.15, 1.54) (Table 2.5.). However, the increase in overall death with each year increase in patients' age (HR: 1.05; 95%CI: 1.01, 1.08) and each score increase in H-score (HR: 0.994; 95%CI: 0.991, 0.997) was very small

**Table 2.5. Covariates associated with all-cause mortality in the Cox proportional model**

| Covariates | Hazard ratio (95%CI) | P-value |
|---|---|---|
| **Type of treatment strategy** | | |
| Surgery | - (reference) | - (reference) |
| Primary endocrine therapy | 2.78 (1.79, 4.33) | P<0.001 |
| **Clinical size** | 1.32 (1.15, 1.54) | P<0.001 |
| **Age** | 1.05 (1.01, 1.08) | P=0.003 |
| **H-score** | 0.994 (0.991, 0.997) | P<0.001 |

**Breast cancer mortality**

When a Cox proportional hazard model was constructed considering type of treatment, age, degree of ER positivity, clinical tumour size, and tumour grade as potential independent prognostic covariates, age (HR: 1.01; 95%CI: 0.92, 1.10), and tumour grade (HR: 0.95; 95%CI: 0.77, 1.19) were not significant prognostic covariates. The stepwise backward elimination method in the Cox proportional hazard model identified that the type of initial treatment strategy, clinical size, and H-score were significantly associated with the breast cancer-related death rate. The results of the Schoenfield residual statistical test revealed that the proportional hazard model assumption was not violated for type of treatment, H-score, and clinical size, and hence time-varying interaction expression was not included in the model (Table 2.6.). Compared to surgery, patients who received PETx were significantly associated with double risk of breast cancer death (HR: 2.15; 95%CI: 1.03, 4.46). A significantly higher risk of breast cancer death was also associated with each one cm increase in patients' tumour size

(HR: 1.49; 95%CI: 1.12, 1.99). However, patients were associated with 1% lower in breast cancer death with each one score increase in patients' H-score (HR: 0.99; 95%CI: 0.98, 0.99).

The subgroup analysis by H-score showed that patients within the 'H-score <250' group, patients who received PETx had a significantly higher risk of breast cancer death compared with patients in the surgical group (HR: 2.59; 95%CI: 1.15, 5.84). However, patients within the 'H-score >250' group, there was no significant difference in beast cancer death between patients who received PETx and surgery (HR: 1.02; 95%CI: 0.21, 4.94).

**Table 2.6. Covariates associated with breast cancer mortality in the Cox proportional hazard model overall and subgroup analysis by H-score**

| Covariates | Hazard ratio (95%CI) | P-value |
|---|---|---|
| ***Overall*** | | |
| **Type of treatment** | | |
| Surgery | (reference) | (reference) |
| PETx | 2.15 (1.03, 4.46) | <0.04 |
| **Clinical size** | 1.42 (1.04, 1.93) | 0.025 |
| **H-score** | 0.99 (0.98, 0.99) | 0.032 |
| ***H-score<250*** | | |
| **Type of treatment** | | |
| Surgery | (reference) | (reference) |
| PETx | 2.5 (1.15, 5.85) | 0.02 |
| **Clinical size** | 1.46 (1.02, 2.08) | 0.03 |
| ***H-score>250*** | | |
| **Type of treatment** | | |
| Surgery | (reference) | (reference) |
| PETx | 1.02 (0.21,4.94) | 0.98 |
| **Clinical size** | 1.26 (0.66, 2.37) | 0.47 |

### 2.4.4. Data management

Of the 672 patients, 564 patients (84%) had complete data recorded in resource use and consequently, their associated costs.

Among the 129, 83, and 14 patients who received non-surgical treatment as their initial, second, and third-lines of treatments, 15 (11.6%), 39 (46.97%), and 3 (21.42%) patients have their time to progression on initial, second, third, and fourth lines of treatment not recorded, respectively. Among the 188, 83, 15, and 5 patients who received second, third, fourth, and fifth lines of treatment, (n=65, 34.58%), (n=44, 50.00%), (n=4, 26.66%), and (n=3, 60.00%) patients have their second, third, and fourth lines of treatment unrecorded, respectively (Table 2.7.). The unrecorded information was managed by the imputation methods described in (section 2.3.4.)

**Table 2.7. Unrecorded data in the variables relevant to this study and methods of data management**

| Variables | Total observations* | Missing (%) | Methods |
|---|---|---|---|
| **Type of treatment** | | | |
| Second treatment | 188 | 65 (34.58) | MNL |
| Third treatment | 83 | 44 (50.00) | MNL |
| Fourth treatment | 15 | 4 (26.66) | MNL |
| Fifth treatment | 5 | 3 (60.00) | MNL |
| **Clinical outcome for non-surgical treatment** | | | |
| Time to progression on first line treatment | 129 | 15 (11.6) | GLM |
| Time to progression on second line treatment | 83 | 39 (46.97) | GLM |
| Time to progression on third line treatment | 14 | 3 (21.42) | GLM |

**(Note)** MNL: Multinomial logistic regression; GLM: generalised linear model
*Including recorded and unrecorded

The median time to progression following initial, second, and third lines of treatments were quite similar in both complete cases and imputed dataset In addition, the proportions of patients who received subsequent lines of treatment in the imputed dataset were quite similar to the ones in the complete case analysis except for exemestane with the proportions of patients who received exemestane as second (24.47% vs. 16%), and third (59.04% vs. 41%) lines of treatments were higher in the imputed dataset as compared to the complete case analysis, respectively (Table 2.8.)

**Table 2.8. Comparison of the complete case and imputed results**

| Variables | Complete case analysis | Imputed |
|---|---|---|
| **Type of treatment** | **n (%)** | **n (%)** |
| ***Second treatment*** | 123 | 188 |
| No treatment | 27 (18.49%) | 27 (14.36%) |
| Megacetrol | 2 (1.37%) | 2 (1.06%) |
| Mastectomy | 5 (3.42%) | 5 (2.66%) |
| Tamoxifen | 8 (5.48%) | 11 (5.85%) |
| Radiotherapy | 1 (0.68%) | 1 (0.53%) |
| Arimidex | 77 (52.54%) | 94 (50%) |
| Exemestane | 24 (16.44%) | 46 (24.47%) |
| Faslodex | 1 (0.68%) | 1 (0.53%) |
| Letrozole | 1 (0.68%) | 1 (0.53%) |
| ***Third treatment*** | 39 | 83 |
| Megacetrol | 3 (7.69%) | 6 (7.23%) |
| Mastectomy | 2 (5.12%) | 2 (2.41%) |
| Tamoxifen | 11 (28.21%) | 19 (22.89%) |
| Radiotherapy | 4 (10.26%) | 4 (4.82%) |
| Exemestane | 16 (41.03%) | 49 (59.04%) |
| Faslodex | 1 (2.56%) | 1 (1.2%) |
| Letrozole | 2 (5.13%) | 2 (2.41%) |
| ***Fourth treatment*** | 11 | 15 |
| No treatment | 1 (9.09%) | 1 (6.67%) |
| Megacetrol | 3 (27.27%) | 4 (26.67%) |
| Mastectomy | 3 (27.27%) | 3 (20%) |
| Radiotherapy | 1 (9.09%) | 1 (6.67%) |
| Faslodex | 3 (27.27%) | 6 (40%) |
| ***Fifth treatment*** | 2 | 5 |
| Radiotherapy | 1 (50%) | 1 (20%) |
| Tamoxifen | 1 (50%) | 1 (20%) |
| Megacetrol | 0 | 1 (20%) |
| Aminogluthamide | 0 | 2 (40%) |
| **Clinical outcomes for non-surgical treatment** | **Median (IQR)** | **Median (IQR)** |
| Time to progression on first line treatment | 114 | 129 |
| | 24 (13, 36) | 25 (14, 36) |
| Time to progression on second line treatment | 44 | 83 |
| | 12 (5, 24) | 11(5, 20) |
| Time to progression on third line treatment | 11 | 14 |
| | 12 (5, 17) | 13.5 (5, 16) |

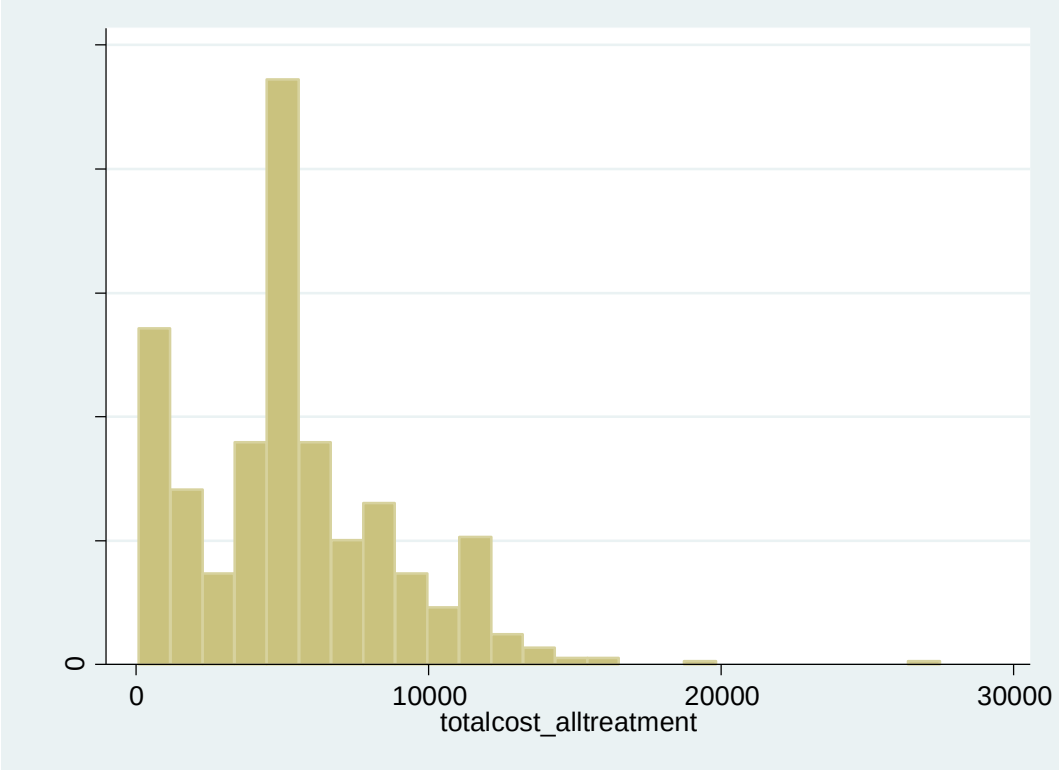
**(Note)** n: number; IQR: interquantile range

### 2.4.5. Treatment cost

The median treatment cost for all patients in the imputed dataset was £5,015.64 (IQR: £2,900.88, £7,068.93) as compared to 5,040.784 (IQR: 2052.95, 6982.22) in the complete case analysis

The total costs showed a highly skewed data distribution with a large number of patients with treatment costs of less than £5,000 and a few patients' treatment costs that ranged from £20,000 to £25,000 (Figure 2.6.).

**Figure 2.6. Distribution of treatment cost during the observed follow-up period**




In the imputed dataset, compared with patients who received surgery (mean cost: £7066.01; 95%CI: £6744.11, £7334.59) as the initial treatment, patients who received PETx (mean cost: £3507.14; 95%CI: £3156.39, £3871.16) (mean difference: -£3558.87; 95%CI: -£4018.11, -£3105.39) had significantly lower mean costs. Similarly,

the PETx group (mean cost: £2783.970; 95%CI: £2479.24, £3135.61) had significantly lower mean costs as compared to the surgical group (mean cost: £7050.35; 95%CI: £6761.206, £7379.31) in the complete cases dataset (mean difference: -£4266.38; 95%CI: -£4690.844, -£3808.75)

The frequency of follow-up visits during the patients' survival time following the initial treatment were higher in the PETx group as compared to the surgical group. The average number of follow-up visits during the patients' survival time were 6.47, 5.04 for the patients in the surgical and PETx groups, respectively (Table 2.9.).

The average number of second line-treatments, including surgical, ETx, and RTx treatments, incurred by patients who received PETx as an initial treatment were higher as compared to the surgical group. In addition, follow-up visits during the patients' survival time were 3.66, 5.86 for the patients in the surgical and PETx groups, respectively.

Moreover, the average number of third and fourth line-treatments, including surgical, ETx, and RTx treatments, incurred by patients who received PETx as an initial treatment were higher as compared to the surgical group

**Table 2.9 Disaggregate results of resource use and unit costs in the imputed dataset**

| | Surgery | PETx | |
|---|---|---|---|
| | **Frequency (mean (95%CI))** | **Frequency (mean (95%C))** | **Unit cost (£)** |
| **Initial treatment** | (n=350) | (n=322) | |
| ***Surgical treatment*** | | | |
| WLE | 0.52 (0.46, 0.56) | 0 | 2635 |
| Mastectomy | 0.45 (0.40, 0.51) | 0 | 2635 |
| Mastectomy+axillary clearance | 0.02 (0.011, 0.048) | 0 | 3398.77 |
| Axillary clearance | 0.30 (0.25, 0.35) | 0 | 2481.01 |
| ***Excess bed days*** | | | |
| WLE | 1.37 (1.20, 1.52) | 0 | 373 |
| Mastectomy | 2.6 (2.34, 2.85) | 0 | 373 |
| Mastectomy+axillary clearance | 0.09 (0.04, 0.18) | 0 | 348 |
| ***PETx*** (Pack) | | | |
| Tamoxifen | 30.22 (27.67, 33.58) | 0 | 2.27 |
| Anastrazole | 31.05 (27.33, 35.14) | 0 | 68.56 |
| ***Adjuvant treatment*** | | | |
| Tamoxifen | 28.9 (26.16, 31.80) | 0 | 2.27 |
| Anastrazole | 4.07 (2.90, 5.52) | 0 | 68.56 |
| Letrozole | 0.003 (NA, NA) | 0 | 3.32 |
| Faslodex | 0.003 (NA, NA) | 0 | 522.41 |
| Delivery of RTx | 8.70 (7.61, 10.31) | 0 | 126 |
| Planning of RTx | 0.35 (0.30, 0.41) | 0 | 796.9 |
| ***Follow-up visit*** | 5.04 (4.82, 5.28) | 6.47 (6.06, 6.93) | 67 |
| **Second treatment** | (n=59) | (n=129) | |
| ***Surgical treatment*** | | | |
| Mastectomy | 0.016 (0, 0.05) | 0.031 (0.01, 0.10) | 2635 |
| ***PETx*** | | | |
| Tamoxifen | 0.05 (NA, NA) | 1.27 (0.55, 2.30) | 2.27 |
| Extemestane | 0.31 (NA, NA) | 4.05 (2.37, 6.86) | 88.8 |
| Anastrazole | 0.19 (NA, NA) | 14.9 (12.18, 17.91) | 68.56 |
| Faslodex | 0 | 0.038 (0, 0.19) | 522.41 |
| Letrozole | 0 | 0.07 ( 0, 0.46) | 3.32 |
| Megacetrol | 0 | 0.31 (0.13, 1.41) | 19.52 |
| ***RTx*** | | | |
| Delivery of RTx | 0 | 0.23 (0, 0.54) | 126 |
| Planning of RTx | 0 | 0.009 ( 0, 0.02) | 796.9 |
| ***Follow-up visit*** | 3.66 (3.25, 4.23) | 5.86 (5.48, 6.40) | 67 |
| ***New admission*** | 1.00 (0, 0) | 1.00 (0, 0) | 169 |
| ***CT frequency*** | 1.00 (0, 0) | 1.00 (0, 0) | 129 |
| ***MDT visits*** | 1.00 (0, 0) | 1.00 (0, 0) | 86 |

**(Note)** PETx: primary endocrine therapy, RTx: radiotherapy, WLE: wide local excision, MDT: multidiscplinary team, CT: computerised tomography

**(Continue Table 2.9.)**

| | Surgery | PETx | |
|---|---|---|---|
| | **Frequency (mean (95%CI))** | **Frequency (mean (95%C))** | **Unit cost (£)** |
| **Third line** | (n=3) | (n=80) | |
| ***Surgical treatment*** | | | |
| Mastectomy | 0 | 0.025 (0, 0.062) | 2635 |
| ***PETx*** | | | |
| Tamoxifen | 0 | 3.23 (1.67, 6.37) | 2.27 |
| Extemestane | 0.33 (0, 0.66) | 3.51 (2.07, 6.07) | 88.8 |
| Megacetrol | 8.66 (0, 14.33) | 0.38 (0.08, 1.06) | 19.52 |
| Faslodex | 0 | 0.025 (0, 0.075) | 522.41 |
| ***RTx*** | | | |
| Delivery of RTx | 0 | 1.25 (0.62, 3.40) | 126 |
| Planning of RTx | 0 | 0.012 (0.003, 0.02) | 796.9 |
| ***Follow-up visit*** | 4.00 (3.33, 5.00) | 4.02 (3.68, 4.53) | 67 |
| ***New admission*** | 1.00 (0, 0) | 1.00 (0, 0) | 169 |
| ***CT frequency*** | 1.00 (0, 0) | 1.00 (0, 0) | 129 |
| ***MDT visits*** | 1.00 (0, 0) | 1.00 (0, 0) | 86 |
| **Fourth-line** | 0 | (n=15) | |
| ***Surgical treatment*** | | | |
| Mastectomy | 0 | 0.2 (0, 0.4) | 2635 |
| ***PETx*** | | | |
| Megacetrol | 0 | 0.26 (NA, NA) | 19.52 |
| Aminogluthamide | 0 | 0.06 (NA, NA) | 24.27 |
| Faslodex | 0 | 2.33 (0, 9.33) | 522.41 |
| ***Follow-up visit*** | 0 | 4.20 (3.66, 4.93) | 67 |
| ***New admission*** | 1.00 (0, 0) | 1.00 (0, 0) | 169 |
| ***CT frequency*** | 1.00 (0, 0) | 1.00 (0, 0) | 129 |
| **MDT visits** | 1.00 (0, 0) | 1.00 (0, 0) | 86 |
| **Fifth-line** | 0 | (n=5) | |
| ***RTx*** | | | |
| Delivery of RTx | 0 | 5 (0, 25) | 126 |
| Planning of RTx | | 0.012 (0.003, 0.02) | 796.9 |
| ***PETx*** | | | |
| Tamoxifen | 0 | 0.2 (NA, NA) | 2.27 |
| Megacetrol | 0 | 0.2 (NA, NA) | 19.52 |
| Aminogluthamide | 0 | 0.4 (NA, NA) | 24.27 |
| ***Follow-up visit*** | 0 | 3.8 (3.4, 4.8) | 67 |
| ***New admission*** | 1.00 (0, 0) | 1.00 (0, 0) | 169 |
| ***CT frequency*** | 1.00 (0, 0) | 1.00 (0, 0) | 129 |
| ***MDT visits*** | 1.00 (0, 0) | 1.00 (0, 0) | 86 |

**(Note)** PETx: primary endocrine therapy, RTx: radiotherapy, WLE: wide local excision, MDT:multidiscplinary team, CT: computerised tomography

**Factors associated with treatment costs**

In the imputed dataset, the results of diagnostic tests for the GLM suggested a normal distribution with log link as the most appropriate model to fit the costing data. The backward elimination approach in the GLM showed that types of treatments, and age were significantly associated with the estimated total direct costs.

Compared to surgery, patients who received PETx had significantly (42%) lower mean costs (mean ratio: 0.58; 95%CI: 0.513, 0.657). Older age was significantly associated with lower costs (mean ratio: 0.98; 95%CI: 0.97, 0.99) (Table 2.10.).

**Table 2.10. Covariates associated with mean total costs in the generalised linear model**

| Covariates | Exponentiated Coefficient (95%CI) | P-value |
|---|---|---|
| **Treatment** | | |
| Surgery | - (reference) | - (reference) |
| Primary endocrine therapy | 0.581 (0.513, 0.657) | P<0.001 |
| **Age** | 0.983 (0.974, 0.992) | P<0.001 |
| **Constant** | 29745.704 (14,875.011, 59,482.653) | P<0.001 |

Similar to the imputed dataset, the results of diagnostic tests for the GLM in the complete dataset suggested a normal distribution with log link as the most appropriate model to fit the costing data with types of treatments, and age were significantly associated with the estimated total direct costs.

Compared to surgery, patients who received PETx had significantly (54%) lower mean costs (mean ratio: 0.46; 95%CI: 0.39, 0.53). Older age was significantly associated with lower costs (mean ratio: 0.98; 95%CI: 0.97, 0.99) (Table 2.11.).

**Table 2.11. Covariates associated with mean total costs in the generalised linear model in the complete case analysis**

| Covariates | Exponentiated Coefficient (95%CI) | P-value |
|---|---|---|
| **Treatment** | | |
| Surgery | - (reference) | - (reference) |
| Primary endocrine therapy | 0.46 (0.39, 0.53) | P<0.001 |
| **Age** | 0.984 (0.974, 0.992) | P<0.001 |
| **Constant** | 23585.09 (11248.35, 49452.6) | P<0.001 |

#### 2.4.5.1. Subgroup analysis by tumour grade

The median treatment cost for all patients in the imputed dataset using tumour grade as one of the predictors was £2948 (IQR: £1181.02, £5576.78).

Compared with patients who received surgery (mean cost: £7066.01; 95%CI: £3579.675, £4084.21) as the initial treatment, patients who received PETx (mean cost: £4026.65; 95%CI: £3806.418, £4284.168) (mean difference: -£199.09; 95%CI: -£575.4654, £129.080) had non-significantly lower mean costs.

The results of diagnostic tests for the GLM suggested a normal distribution with log link as the most appropriate model to fit the costing data. The backward elimination approach in the GLM showed that types of treatments, tumour grade, and age were significantly associated with the estimated total direct costs.

Compared to surgery, patients who received PETx had significantly (22%) lower mean costs (mean ratio: 0.78; 95%CI: 0.68, 0.89). Older age was significantly associated with lower mean costs (mean ratio: 0.97; 95%CI: 0.95, 0.98). Compared to patients with low tumour grade, patients with high tumour grade had significantly lower mean costs (mean ratio: 0.65; 95%CI: 0.54, 0.79) (Table 2.12.).

**Table 2.12. Covariates associated with mean total costs in the generalised linear model in the subgroup analysis**

| Covariates | Exponentiated Coefficient (95%CI) | P-value |
|---|---|---|
| **Treatment** | | |
| Surgery | - (reference) | - (reference) |
| Primary endocrine therapy | 0.78 (0.68, 0.89) | P<0.001 |
| **Age** | 0.97 (0.95, 0.98) | P<0.001 |
| **Tumour grade** | | |
| Grade 2 | 0.92 (0.82,1.03) | 0.179 |
| Grade 3 | 0.65 (0.54, 0.79) | P<0.001 |
| **Constant** | 59574.92 (25299.25, 140287.60) | P<0.001 |

## 2.5. Discussion

### 2.5.1. Main findings

Overall, the proportions of patients who received surgery and PETx were approximately the same in the cohort. The results of this chapter showed a predominance of ER-positive tumour, larger tumour size, and older age for patients who received PETx compared with those received surgical treatments. Across the patients' treatment pathways, ETx and surgery were the most common subsequent lines of treatments prescribed after first-line PETx and surgical treatment failure, respectively.

A significant difference in overall and breast cancer death between PETx and surgery was observed and surgery was associated with a lower breast cancer death rate. Moreover, a significant difference in direct costs was observed between both treatment strategies with surgery was associated with higher breast cancer death rate and cost compared with PETx. In addition, the subgroup analysis by H-score over 250 showed that patients who received surgery or PETx had similar breast cancer death rate.

### 2.5.2. Common initial treatment strategies for older women with primary breast cancer

Despite the lack of guidelines or standardised patient pathways described in the literature for treating older women in clinical practice (45,47), this study identified the treatment pathways within a single institution providing long-term outcome for around four decades. Within these treatment pathways, the proportions of patients who were offered PETx or surgery were approximately the same. This could be partly explained due to the popularity of using PETx during 1990 as an alternative to surgery due to frailty issue, or patient preferences in the UK (80,111,219). Given that this cohort study is quite representative of the older women with primary breast cancer in the UK,

surgery and PETx represent the most common treatment strategies available for older women with primary breast cancer in the UK.

### 2.5.3. Comparison of the cohort treatment with guidelines and national audits

Except for the adjuvant CTx proportions, the treatment patterns in the cohort database were consistent with the ones in the national guidelines and audits. PETx (37% vs. 41%), adjuvant ETx (88% vs. 82%-98%), RTx (49% vs. 30%-60%) proportions in this database were comparable with other national guidelines and audits. PETx is widely used in older women despite evidence of poor locoregional control (5). However, the rationale behind adopting this treatment was slightly different across different audits. In Wyld, *et.al*. (2005), its use was justified by patients being ER-positive and had a limited life expectancy or severe comorbidities (111), whereas in the cohort study, it was justified by being unfit or patients' choice.

Adjuvant ETx is used in majorities of older patients with ER-positive status. Furthermore, there is a tendency to omit adjuvant RTx after BCTx in older patients (Section 1.3.4.1.). Older women with large breast tumours (>5cm) and high axillary stage may benefit from post-mastectomy radiotherapy (220).

There is a tendency toward performing less extensive axillary surgery in older women, such as SLNB (221). The rate of axillary surgery in the cohort was comparable to the North Trent audit. However, the rate of SLNB was low as compared to the cohort database. This low rate was explained by the fact that SLNB was not common in the clinical practice in the UK (222). In addition, the previous audits did not report the percentages of patients who underwent axillary clearance following SLNB who further underwent axillary clearance (111,136). A review by Wada and Imoto. (2008) to identify the prevalence of SLNB micrometastases showed that SLNBs were positive in 21% to 47% of patients with primary breast cancer (136,223).

Although the CTx rates were very low as compared to the majorities of the previous guideline and national audits, it was only consistent with the Wyld, *et.al.* (2004) study (111). The low rate was only justified by limited evidence for the role of adjuvant CTx in the treatment of older women with breast cancer. CTx in this cohort was offered for patients who were fit with moderate/ poor prognosis (NPI> 3.4) and ER-negative status. In the clinical practice, CTx was offered for patients with NPI>4.4 and ER negative (Wyld, 2004) (111), and thus, 157 patients were eligible to receive CTx in this cohort but they did not receive it.

### 2.5.4. Effectiveness of surgery and PETx in older women with primary breast cancer

#### 2.5.4.1. Secular changes with time

This database described the evolving changes in the treatment and clinical outcome over four decades from 1973 until 2010. Patients diagnosed in recent decades (after 2000) were older (median age: 78 years vs. 74 years) and have smaller tumour size (median clinical size = 2.5 cm vs. 3 cm) as compared with those who were diagnosed in the older decades (before 1990) (80).

In addition, ER status was routinely measured in 1990 and become a standard in recent (after 2000) year compared with previous decades. ER/PR/HER2 status was routinely measured in 2007 with 13.4% and 8.2% were found to have triple negative and HER2-positive disease, respectively. Axillary surgery become a standard part of the surgery in the recent decade 2000 (0.8%, 44.3%, 87.7% in 1970, 1990, after 2000, respectively) (80).

PETx was more frequently used in the earlier period (43.6%, 59.9%, 41.1% in 1970s, 1990s, after 2000s, respectively). There was a higher trend toward having BCTx in recent decade (7.8%, 27.7%, 39.1% in 1970s, 1990s, after 2000s, respectively) and a

lower trend to undergo mastectomy (92.2%, 72.3%, 60.9% in 1970s, 1990s, after 2000s, respectively). There was a gradual move towards giving more adjuvant therapies in the recent decade. (Adjuvant ETx: 0.8%, 44.3%, 87.7% 1970s, 1990s, after 2000s, respectively), (Adjuvant RTx: 0.8%, 47.1%, 55.4% 1970s, 1990s, after 2000s, respectively), (Adjuvant RTx after Mastectomy: 2.5%, 2.09%, 25.95% 1970s, 1990s, after 2000s, respectively), (Adjuvant RTx after WLE: 10%, 9.59%, 49.19% 1970s, 1990s, after 2000s, respectively). Patients were offered AIs as a PETx since it became available in 1995 as an alternative to tamoxifen with contraindications (e.g. thromboembolism) (80).

There were a significant improvement in the short (regional and local recurrence) and long-term (overall and breast cancer death) clinical outcomes in the recent decades; (LR rate per year: 2.9%, 1.8%, 0.5% in 1970s, 1990s, 2000s, respectively, $p<0.001$). (Metastases rate per year: 3.1%, 2.8%, 1.5% in 1970s, 1990s, 2000s, respectively, $p<0.001$). Furthermore, the 5-year breast cancer and overall survival rates were significantly improved over the four decades (5-year breast cancer survival: 81% vs. 91% before and after 2000, respectively, $p<0.001$). (The 5-year overall survival: 56% vs. 71% before and after 2000, respectively, $p<0.001$ (80). Since the recent cohort (i.e. 2000s onwards) reflects the clinical practice, the analysis was restricted to the recent decades.

#### 2.5.4.2. Comparison with previous literature

This study showed significantly higher overall mortality and deaths from breast cancer following PETx compared with surgery ($P<0.001$). This was consistent with four observational studies comparing the use of PETx against surgery (55,61,69,70), which were included in a review of 29 observational studies (51), and showed that PETx was associated with both higher overall and breast cancer death rates compared with surgery. Moreover, a previous analysis reported by Syed *et al.* (2011) using the same

database with this study to compare the breast cancer related death between surgery and PETx for patients with ER-positive status, and found a significant difference in breast cancer death in favour of surgery in patients with H-score less than 200, while it found a non-significant difference in breast cancer death between surgery and PETx in patients with H-score over 250 (69).

The available observational studies compared the overall and breast cancer death between surgery and PETx and none compared the life year gained (LYG). Since none of these previous observational studies aimed to inform the cost-effectiveness of surgery and PET, they did not compare the LYG between surgery and PETx; LYG considers how long patients survived after receiving the initial treatment, and this outcome measure can be incorporated later into an economic evaluation to assess the cost-effectiveness of using the treatment strategies in older women with primary breast cancer.

#### 2.5.4.3. Factors associated with breast cancer survival and progression

This study found that treatments, clinical size, degree of ER positivity, and age, were significant predictors of overall survival; of which, smaller clinical size, higher degrees of H-score were associated with higher overall and breast cancer death, and breast cancer progression, while PETx was associated with higher death and progression. . Older age is associated with more comorbidities (189,190), shorter life expectancy (131), and thus higher overall death rates. Previous literature had also found that patients with strong ER status expression (i.e. higher H-score) were associated with lower breast cancer death rates (Section 1.2.3.2.) (6). Surgical treatment was associated with better breast cancer survival and progression (51).

Tumour size, axillary stage of lymph nodes, and tumour grade have been identified as prognostic factors for overall and breast cancer survival in several survival prognostic models (224-226). However, given that the pathological size and tumour grade were

only available for older women who underwent surgical treatment, the significance of clinical size and tumour grade based on needle core biopsy has been tested instead. This study showed a statistically significant correlation between small clinical size of the tumour and better breast cancer survival rates. However, tumour grade did not show a significant association with breast and overall death rates, and therefore, was not included within the model. These findings were consistent with previous RCTs conducted in older women with primary breast cancer (73,74).

However, there is a lacking of some patients' characteristics recorded in the database such as comorbidities, ethnicity, and frailty index, which could be predictors of overall survival, and thus may potentially bias the overall survival results since they were not adjusted for in the analysis.

### 2.5.5. Costs of surgery and PETx in older women with primary breast cancer

#### 2.5.5.1. Distribution of costs

The current study showed a wide variation in the total direct costs incurred by the individual patients, which was illustrated by right-skewed distribution. This indicates that few patients utilised more health care resources than the average individuals, and consequently, had higher associated costs compared with the whole cohort group.

#### 2.5.5.2. Variation in health care resource use and cost estimation

The comparison of the current results with the findings reported from previous studies conducted in countries other than the UK was difficult due to their using different health care systems with different currencies to estimate costs. Although the current cost findings were consistent with previous studies conducted in the area of breast cancer, the costs estimated from the current study were lower compared with the previous literature.

In this current study, the cost associated with having a local or regional recurrence (£6519.49) as the first event was higher compared with metastasis (£6234.23). This may be because patients with metastasis in this cohort study did not live for a long-time compared with patients with local recurrence, and thus did not incur the additional costs in terms of follow-up and drug prescription compared to patients with locoregional recurrence. Moreover, some of the patients who have a locoregional recurrence eventually progressed to metastasis, and thus the additional costs of treating metastasis incurred by those patients.

Karnon *et al*. (2005) study demonstrated that 5-year aggregated costs for patients whose first event was locoregional or contralateral tumour were £24,000 (95%CI: £36,804, £31,659) while £16,640 (95%CI: £15,000, £20,000) were incurred for patients with metastasis. Inflating these costs to prices of year 2014 using the National Health Service hospital and community inflation index from the PSSRU would be £30,012, £20,808, respectively (183).

These differences in the estimated costs in the current study compared with that of Karnon *et al*. may be attributed to the differences in patients' age included in both studies, and thus may utilised different resource use. Since older women have a longer mean length of stay as compared to younger population due to higher rate of comorbidities and surgical complications and thus would incur higher inpatient costs (Section 1.4.2; 1.4.4). In addition, the population included within the Karnon study was only patients who received surgery as an initial treatment for locoregional recurrence whereas in the current study patients were offered either PETx, which is the less-expensive treatment, or surgery as an initial treatment (183). Furthermore, the Karnon study included more detailed resource-use associated with metastatic diagnosis, such as liver and bone scan, treatment, including further excision for brain, bone, neck, and lung metastasis, and treatments for metastatic complications, such as pleural effusion

and blood transfusion (183). These resources were not accounted for in the current study due to lack of information about them in the database, and thus, this may contribute to the underestimation of the metastatic costs as a first event or subsequent events after locoregional recurrence. Finally, it was assumed that older women did not undergo a breast reconstruction in the current study, which also may contribute to low recurrence costs compared with the Karnon study.

Thomas *et al*. (2009) reported that the mean direct costs associated with treating recurrent breast cancer were £25,186 (inflated to 2014) (184). These higher estimated costs as compared to the ones estimated from the current study can be attributed to a number of issues. First, primary care costs contributed to 30.3% of total costs, including GP appointments, GP calls, hospice visits and nights, and GP prescriptions (184). These resources were not accounted for in the database since GPs had a minor role in treating patients with primary breast cancer in the current study. Second, Herceptin drugs were used for few patients in the Thomas study. These drugs are associated with high costs that would increase the total costs of treating patients with breast cancer.

Hall *et al.* (2015) concluded that costs over 15 months were £12,595 (£12,951 inflated to 2014) (185). However, this study did not provide a summary of the resource-use category utilised, and thus, hinders comparing the resource-use utilisation, and hence their associated costs with the current study.

Remark and Brazil (2004) showed that the costs were £12,502 (£18,482 if inflated to 2014). The difference in costs between this study and the current study can be attributed again to detailed specification of the resource-use associated with treating metastatic breast cancer (186). In the Remark and Brazil study, the resource categories were broken down into two categories. First, active treatment, including

medications, scanning, laboratory tests, and outpatient visits (186). Second, supportive and end of life care, including treatments aims to alleviate pain and symptoms of the disease, such as blood transfusion, in addition to the increased frequency of hospital stay and outpatient visits in these two categories (186). Considering the costs associated with both categories would justify the high costs of metastatic disease.

Another two studies also estimated the costs associated with metastatic breast cancer. Richards *et al*. (1993) conducted a study on 50 patients in the UK who were diagnosed with metastasis and identified retrospectively from their medical notes in a hospital setting. This showed the costs associated with metastasis were £7620 (£14,125 if inflated to 2014) (182). Wolstenholme *et. al.* (1998) conducted the other study to prospectively analyse 137 patients diagnosed with breast cancer in a hospital for 4 years in the UK, which showed that the costs estimated for stage I and stage IV were £3,576 (£7216.28 if inflated to 2014) and £6,590 (£13,308.30 if inflated to 2014), respectively (187). Although the results were slightly lower compared with previous literature since they did not include the GP follow-up and palliative care costs, still these two studies showed higher costs compared with the costs estimated in the current study (187).

#### 2.5.5.3. Factors associated with the costs

Overall, this study found that type of treatment, age are strong predictors of costs. Older age predicted lower costs. This may be explained by the fact that patients of younger age would live longer, and thus, accumulate more costs. These findings were in concordance with previous studies. Hall *et al*. (2015) examined the factors that predict direct total costs in patients with breast cancer in the UK and showed older age to be associated with lower costs in an univariate analysis (185). Moreover, Thomas *et al*. (2009) showed that older age was associated with lower costs (184). None of the

previous studies considered type of treatment as one of the covariates in the analysis since the main treatment used in the previous studies was surgery for treating locoregional recurrence and non-surgery for treating metastasis, and thus the impacts of the types of treatment on the costs were not documented in previous literature (184,185).

Previous observational studies showed that lymph node status, tumour grade, HER2, and multiple deprivations were predictors of total costs (185). These factors were not accounted for in the current study, because they were not recorded in the database or did not have complete information for all patients, and thus, the impact of treatment and age on the costs may be biased since other predictors were not accounted for in the regression model.

The patients who received surgery were associated with higher mean costs compared with those who received PETx overall and for patients within unknown and ER-positive status groups. This may be attributed to the higher costs of surgical procedure s compared to the PETx therapy.

#### 2.5.5.4. Factors that could impact the length of hospital stay and associated costs

There is a lack of comorbidities index recorded in the database. Comorbidities have an impact on surgical complications and prolonging length of stay that could consequently influence the resource utilisation and associated costs (Section 1.4.4.) (130).

HRG is generated based on the type of procedure, diagnosis, LOS, complications, co-morbidity, discharge method, age and gender (227). Some HRGs are splitted by complication and comorbidity by use of a Complication and comorbidity (CC) list (228).

HRG codes are assigned costs in the NHS reference based on different complication and comorbidities scores. These CC list allows identification of other comorbidities that resulted in additional resources being used by patients, and also as a way of incorporating severity and complexity within the design of the HRGs. Some comorbidities may be a major complication for some procedures whilst not for others. The HRG is generated by summing the score of all comorbidities, which appear on the CC list. Major CCs have a value of two and all other CCs have a value of one. (228) HRG codes with higher CCs scores are associated with higher costs and therefore, the lack of CCs will underestimate costs since the older women are at higher risk of surgical complication and comorbidities as compared to younger population.

### 2.5.6. Strengths and limitations

Based on the existing knowledge, this was the most-recent cohort study that has estimated the total direct costs of treating older women with primary breast cancer in secondary care setting using a single source of database containing a sample that is quite representative of the primary breast cancer population in the UK in terms of tumour characteristics, age, and ethnicity. The study cohort was a consecutive series, which included all patients who came to receive diagnosis and treatment in the clinic, and majority of their treatment pathways, including inpatient procedure, outpatient prescriptions were recorded, and thus ensure the generalisability of the cost-effectiveness results. Furthermore, this was the first study in the UK to estimate the total costs associated for older women with primary breast cancer longitudinally considering all patients' treatment pathway resources from the date of diagnosis until death or loss to follow-up in order to provide a clear insight on the economic burden of breast cancer patients incurred by the NHS.

In the database, all the older women, including patients from the East Midlands population, who were presented to and managed in the clinic according to predefined

treatment guidelines since 1973 were consecutively included in the database (15,80). Therefore, this cohort is a good representation of the entire population of breast cancer women in the East Midlands who access medical treatments.

The demographic of the East Midlands population obtained from the latest census appeared fairly typical of the UK except for deprivation and enhance the generalisability of these results to the UK population. The East Midlands has a slightly larger percentage of White ethnic groups (89%) compared with Wales and England (87%) (229). Nottingham was ranked as the 10th most deprived area in the UK according to the Department for Communities and Local Government (230). In terms of tumour characteristics, the patients recruited within the cohort study are quite similar to patients with primary breast cancer in England. A total of 49,994 women were diagnosed with breast cancer in the UK in 2007 (231), of which 44,513 (89%) were diagnosed with primary breast cancer. In addition, 34,211 (68%) were symptomatically detected and surgically treated (231), of which (24%) were aged over 70 years old. Amongst patients who were symptomatically diagnosed with breast cancer over 70 years old and surgically treated (231), 79% had ER-positive and 38% tumour size less than 2 mm, which are comparable to the current database where 78% of the patients who received surgery had ER positive status (231) and 38.5% of the patients had tumour size less than 2 cm. Given that information regarding the tumour characteristics for older women with primary breast cancer who received PETx in the UK is scarce, the comparison was only limited to patients who were surgically treated (231).

This study has important implications for practice in the context of further health economic analysis and modelling in older women with breast cancer. First, the costs estimated in this current study alongside the life-year gain can be combined later into a cost-effectiveness ratio, which can inform resource allocation decisions. Second, the treatment pathways identified from this cohort database could form the basic ground

for further economic modelling which may combine data from different resources to evaluate the cost-effectiveness of using different treatment strategies in older women with primary breast cancer.

Some limitations have been encountered in the current study. Due to the retrospective nature of the data, complete identification of all resources required to fully estimate the total costs could not be attained. This is because some of the health care resources were not recorded in the database. For example, frequency and dose of non-surgical treatments, including ETx, RTx, or CTx either as initial or subsequent lines of treatments, frequency of follow-up visits in outpatient setting, or frequency of follow-up visits in the primary care setting for patients who were referred back to the GP.

Furthermore, there was under-recording of the time to progression on non-surgical treatments and type of subsequent lines of treatments in the database. Estimating of total costs requires the estimate of the subsequent treatments, medication prescriptions, and follow-up frequency. Time to progression is important to estimate follow-up frequency and non-surgical prescription frequency while second, third, and fourth-line treatments are important to estimate the costs associated with those treatments. If one of these data points were missing, the whole cost for the individual pathways would be considered missing, thus, assumptions have been made to correct for unrecorded and under-recorded resource use by using clinical expert opinion and some statistical modelling techniques. Moreover, resource use related to palliative and end-life treatment for patients with metastasis, including diagnostic tests, treating disease complications were not recorded and consequently, estimated costs for metastatic disease in the current study may be underestimated, and accordingly the total direct costs in the current study.

Since not all the covariates required to predict the missing time to progression and type of treatments were accounted for, either because there were not recorded (such as the frailty index) or because the data were not recorded for all patients (such as tumour grade or axillary stage), thus the regression imputation model might be inadequately specified if not all the covariates were included to predict the observations. Although the limitation of the regression imputation approach, the conclusion that the surgery is associated with higher costs as compared to PETx did not change when a complete case and subgroup analyses were also conducted.

There are some important variables that were not recorded in the database and could bias the LYG, and their resource use estimates, including frailty, ER status, tumour stage, and tumour grade. Patients who are unfit due to a higher level of comorbidities would results in lower life expectancy due to higher risk of overall death from other diseases, and thus, resulted in lower LYGs (Section 1.4.4.). Since patients in this database who were offered PETx were more likely to be unfit for surgery with lower life expectancy and thus, comparing these two groups regardless their fitness status will introduce a bias in favour to surgery.

ER status was not universally tested in the early decade, and it has been introduced since 1990 (80). Using a subset of the cohort, (i.e. the recent decade) still the ER status of some patients was not recorded (2%). Previous studies showed that 20% of older women would have ER-negative breast cancer, which will not respond to ETx (Section 1.3.2.2.). In addition, patients with ER-positive status experienced lower breast cancer death as compared to patients with ER-negative status, and hence, not matching these groups will introduce a bias in favour to surgery (6).

Axillary stage and tumour grade are also main predictors for breast cancer death. Patients with higher tumour stage and grade are associated with poor prognosis and

higher breast cancer death results in lower LYG (6). Complete recording of these variables are important to provide a robust estimate of breast cancer death and LYG adjusted for the covariates that influence their estimates. In addition, axillary stage is part of the tumour stage components. Although tumour size and presence of metastasis were recorded, axillary stage was not completely recorded, and thus tumour stage could not be measured for all patients. Tumour stage is an important prognostic factor and guides the treatment decision (232). Furthermore, it is important when there is a need to merge the data with other sources with similar tumour stage, fitness, and ER status since patients with different tumour stage, fitness, and ER status would have different prognosis in terms of breast cancer progression and survival.

## 2.6. Conclusion

Since surgery and PETx are commonly used as initial treatments of primary breast cancer in older women in the UK, PETx may have a potential role in treating those groups of patients. Given that PETx was associated with higher breast cancer death and lower mean costs compared with surgery within groups of patients with ER-positive status. In addition, it has been suggested in the literature that older women with breast cancer of ER-positive status are more susceptible to respond to PETx (Chapter 2). Syed *et al.* (2011), which showed that within older women patients aged over 70 years with ER-rich tumour, those who received PETx achieved an equivalent breast cancer survival rate to patients who underwent surgery (69). Therefore, PETx could be a cost-effective treatment for patients with H-score over 250. It is worth further investigating the potential cost-effectiveness of PETx compared with surgery in these groups of patients by conducting a cost-effective analysis comparing PETx against surgery in older women with primary breast cancer.

The censoring issue is a challenging limitation when conducting an economic evaluation alongside observational studies, alternatively an economic modelling approach can possibly extrapolate the survival time for patients who have incomplete follow-up duration.

# Chapter 3. A systematic review of modelling methodology used to assess the cost-effectiveness of different treatment strategies for postmenopausal women with primary breast cancer

## 3.1. Introduction

PETx and surgery are the most common treatment strategies offered to older women with primary breast cancer in clinical practices in the UK. Comparing with patients who received surgery as the initial treatment strategy, those who received PETx were observed to have lower breast cancer death rate and mean costs (Chapter 2). Therefore, PETx could be a cost-effective treatment for patients with H-score over 250. To optimise the treatments for older women with primary breast cancer, a further cost-effectiveness information, in particular the specific subgroup of patients will be helpful to inform treatment decision making. However, the lifetime data were not available for some patients due to the censoring issue, i.e. patients were still survived at the end of the study period. Alternatively, economic modelling approaches can be used to estimate (simulate) the costs and outcomes beyond the follow-up end point (233).

Currently, there is a lack of economic evaluations comparing the use of PETx against surgery as an initial treatment in older women with primary breast cancer, and most economic studies assessed treatments in younger population. Modelling approaches have been used for assessing different adjuvant treatment strategies for postmenopausal primary breast cancer. There are two systematic reviews of economic evaluations conducted in postmenopausal women with primary breast cancer (234,235). The former aimed to summarise the cost-effectiveness results associated with different endocrine therapeutic strategies (head-to-head comparison) (234), while the latter aimed to review and summarise the cost-effectiveness results for trastuzumab used as an adjuvant treatment for HER2-positive early breast cancer (235).

These two systematic reviews provide a useful overview of the outcomes of CEA of adjuvant endocrine therapies and adjuvant trastuzumab in postmenopausal women with primary breast cancer, respectively. However, these systematic reviews were not conducted specifically for postmenopausal women. Moreover, they did not compare the different types of treatment strategies. In addition, neither of these two reviews summarised the key parameters of the models – such as cost and resource-use data, and sensitivity analysis – that are necessary to inform the model construction (234,235).

Since there is a lack of economic evaluations conducted in older women with primary breast cancer, a comprehensive literature review of the economic models that have been used previously conducted in postmenopausal women can support the design of an economic evaluation based on an economic model for assessing the cost-effectiveness of using different treatment strategies in older women with primary breast cancer.

Postmenopausal women are closer to the age of target patients in this study, and they generally receive only surgery as an initial treatment followed by adjuvant therapy (as recommended by guideline), and share similar clinical pathways and outcomes to older women.

Therefore, a systematic review was conducted to summarise the modelling methodology used to assess the cost-effectiveness of different treatment strategies for postmenopausal women with primary breast cancer, including the types of model, health states, key parameters, types of resources, cost type, and types of sensitivity analysis that were used to test the robustness of the results, and further explored whether any study conducted subgroup analysis of older patients.

## 3.2. Aim and objectives

This systematic review aimed to summarise and critique the modelling methodology from published economic evaluations that assessed the cost-effectiveness of different treatment strategies in postmenopausal women with primary breast cancer.

The objectives include:

1. To retrieve economic evaluation studies that used decision analytical modelling approaches to evaluate the cost-effectiveness of different treatment strategies in postmenopausal women with primary breast cancer.

2. To summarise the frameworks of the retrieved economic evaluations, including model design, benefit and outcome measure data, cost and resource-use data, type of economic evaluation, and type of sensitivity analysis.

3. To identify the health states associated with surgical pathways in older women with primary breast cancer.

## 3.3. Method

### 3.3.1. Search strategy

An electronic database search was conducted by applying structured search strategies in different electronic databases of medical literature, including the NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) database in the Centre for Reviews and Dissemination (CRD), Cochrane Library, Ovid Medline and Ovid in process Medline (1964 to March 2014), PubMed® (1972 to March 2014), and Ovid EMBASE® (1974 to March 2014). The search strategies were constituted of key words related to primary breast cancer, different interventions (surgery, RTx, CTx, ETx, and trastuzumab), and outcomes (survival, recurrence, adverse effect, and quality of life) using both Medical Subject Heading (MeSH) and free texts. The search was limited to English language and humans. In addition, the economic evaluation filter was used in Medline, PubMed, and EMBASE databases (Appendix 6.)

### 3.3.2. Study selection

Full economic evaluations (i.e. cost-effectiveness, cost-utility, and cost-benefit analysis) and cost minimisation studies that compared different adjuvant treatment strategies in postmenopausal women with primary breast cancer were included in this review. Studies excluded from this review were those that were partial economic evaluation studies (i.e. cost of illness study, outcome description, cost description, outcome and cost descriptions), included only premenopausal patients, patients diagnosed with other breast cancer conditions (such as metastatic breast cancer, locally advanced breast cancer, recurrence of breast cancer, unconfirmed breast cancer, or non-invasive breast cancer), and were not full-text publications (e.g. conference abstract).

After screening the abstracts, the full texts of eligible studies were assessed and only studies which included data for the subgroups of females, postmenopausal patients,

and patients with primary breast cancer were included in this systematic review (Table 3.1.).

**Table 3.1. Exclusion and inclusion criteria for selecting economic evaluations of different treatment strategies in the systematic review**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Condition** | Early breast cancer | Only metastatic breast cancer |
| | Primary breast cancer | Only locally advanced breast cancer |
| | Operable breast cancer | Only recurrence of breast cancer |
| | Stage I-II breast cancer | Unconfirmed breast cancer |
| | | Only non-invasive breast cancer |
| | | Other diseases |
| **Population** | Female or mixed gender | Only male |
| | Postmenopausal or mixed age | Only premenopausal |
| **Intervention** | Surgery as primary Tx plus | Head-to-head comparison |
| | adjuvant therapies: | Test to determine response after treatment |
| | Endocrine therapy | Procedures for diagnosis of breast cancer |
| | Chemotherapy | Preventive strategy |
| | Radiotherapy | Preoperative therapy |
| | Biological therapy | Nursing or rehabilitation care |
| **Comparators** | Surgery as primary Tx plus | Treatments or prevention for adverse drug events |
| | other adjuvant therapies or | Treating of cancer complication |
| | none | Follow up strategy |
| **Outcome** | Clinical outcomes such as recurrence, survival, adverse events or complication, or quality of life | Other outcomes<br>Prevalence |
| **Type of study** | Full economic or cost-minimising analysis studies included decision economic models | Partial economic studies (cost of illness study, outcome description, cost description, outcome and cost descriptions, cost analysis)<br>Literature review<br>Clinical trials, observational studies |
| **Publication type** | Full-published studies | Conference abstract or proceeding, abstract without full article<br>Letter to editors, editorial, commentary, and news |
| **Language** | English | |
| **Species** | Human | Animal |

### 3.3.3. Data extraction

Three types of information were extracted from reviewing the selected studies, including: (1) economic study design, i.e. the scope of decision analytical model including perspective, country, population (age and any subgroup analysis), time horizon, treatment strategies, and benefits; (2) characteristics of economic models, i.e. type of model, disease states, cycle length, and type of sensitivity analysis; (3) data sources used in the economic model, i.e. types of effectiveness, cost and resource use, and utility data.

### 3.3.4. Quality assessment

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (236) and Philips (237) checklists were used to evaluate the five quality elements of selected studies, namely model structure, data sources and costs, uncertainty of the model results, result presentation, and interpretation.

CHEERS provides the most updated checklists developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force members, which reviewed the previously published checklists related to the reporting of economic evaluations to provide standardised recommendations to optimise the reporting of health economic evaluations (236). This checklist has been published in journals, such as Value in Health, PharmacoEconomics, BMC Medicine, and BMJ, which represent the largest repositories of economic evaluations and are widely read by the medical community. CHEERS is a 24-item checklist, from which a 63 sub-question checklist was derived and used in this review to judge the quality of the structure of the economic models, the quality of resource use and cost data, the quality of assessing the uncertainty, and the way of interpreting the results. This structure and narrative summary can offer some guidance to inform the design of the economic evaluation

framework by reporting other aspects of an economic evaluation framework (i.e. cost, resource use data, primary outcome measure).

Philips checklist is a 15-item checklist, from which a 58 sub-question checklist was derived. The Philips checklist is based on a systematic review conducted by Philips *et al.* (2006) of previously published guidelines developed, particularly to assess the quality of decision analytical models. Some questions in the Philips checklist overlap with questions in the CHEERS checklist, but the Philips checklist addresses more details regarding the modelling methodologies, and thus 16 (question nos. 10, 15, 16, 22, 31, 34, 36-40, 60, 64, 67, 69, 70) out of the 58 questions developed by Philips *et al.* (2006), which were not covered by CHEERS guidelines for assessing the quality of the economic models, was used to judge the quality of the structure of the economic models included in this review (237). The other 42 questions in the Philips checklist were covered already in the CHEERS checklist, and therefore, were not used in this review.

Overall, these 79 questions (63 derived from the CHEERS guideline and 16 derived from the Philips checklist) were categorised into four categories, namely model structure, data source, uncertainty, result interpretation and presentation. Questions 1 to 23 related to the structure of the model ranging from detailed justification of the decision research problem to detailed justification of the appropriate choice of model types, cycle length, and time horizon. Questions 24 to 57 related to the quality of the data incorporated in the model, the source of the data, the method used to incorporate the data in the model, and methods and source used to estimate resource use and costs. Questions 58 to 70 evaluate whether economic evaluations are used for sensitivity analysis to address the four principle types of uncertainty, i.e. methodological, structural, parameter, and heterogeneity uncertainty. Questions 71 to

79 also assess how the results were presented and interpreted and how it is generalisable to the clinical practice (Appendix 7.).

### 3.3.5. Summary of results

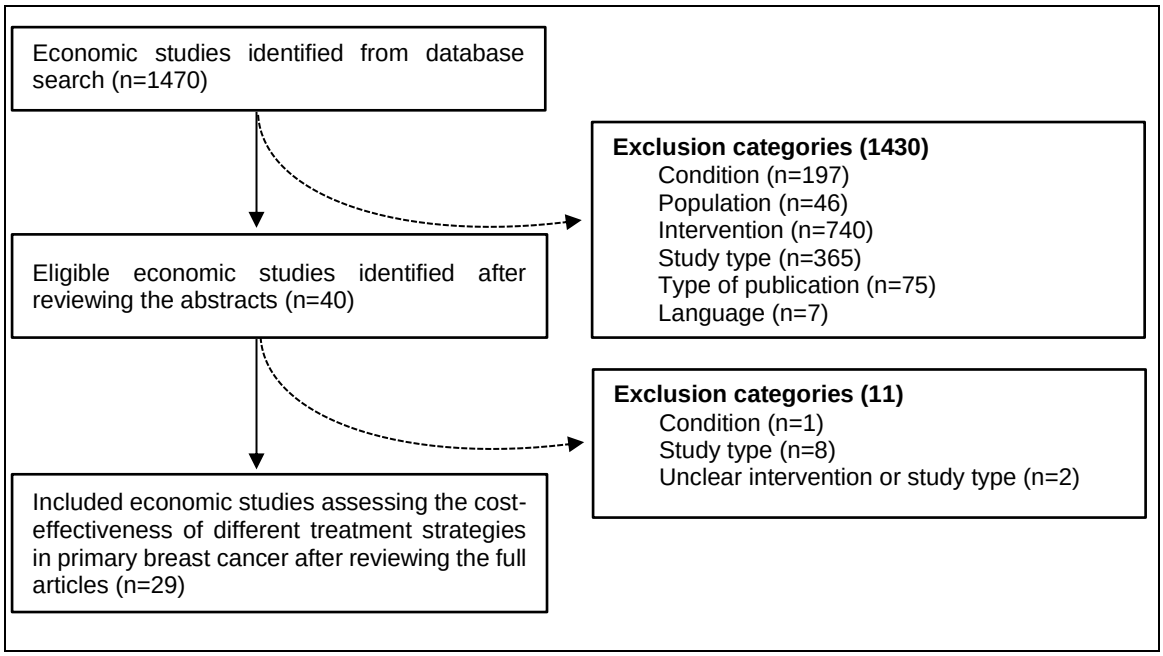
This systematic review reported a descriptive summary of the selected studies, including characteristics of economic evaluations, model design, and quality assessment of the economic models. In addition, a narrative description of the characteristics of economic models stratified by different initial or adjuvant treatment strategies, and further stratified by age groups, was also reported in this review.

## 3.4. Result of systematic review of economic evaluations

### 3.4.1. Selection of included studies

Overall, 1,470 articles were identified from the electronic database search; of which 1,430 studies were excluded after preliminary screening of titles and abstracts. The full texts of the 40 remaining articles were assessed and total of 29 articles that matched the inclusion criteria were included in this review (.). In total, 1,441 articles were excluded due to non-primary breast cancer conditions (n=198), premenopausal patients (n=46), similar adjuvant breast cancer treatments (n=740), non-full economic studies (n=373), not full-text publication (n=75), and non-English language (n=7).

**Figure 3.1. Selection of economic studies assessing the cost-effectiveness of various adjuvant treatment strategies for treating postmenopausal women with primary breast cancer**




### 3.4.2. Characteristics of included economic evaluations

The included economic studies were conducted in several countries, including UK (n=3) (161,165,238), USA (n=12) (162,163,166,167,169,170,239-244), Canada (n=3) (168,245,246), and nine other countries (n=11). Except for one study (247), all included studies reported the age of the population analysed in the model, ranging from 40 to more than 85 years old; of which three studies reported subgroup analysis for patients over 65 years old (166,246,248) (Table 3.2.).

Except for five studies (162,163,243,244,249), 24 studies mentioned the perspective of the economic evaluation, which included societal (n=10) (166,167,169,241,242,247,250-253), health care providers' (n=11) (161,164,165,170,238,245,248,254-257), direct payer's (n=2) (168,246), payer's and societal (n=1) (239) perspective (Table 3.2.).

***Type of treatment strategies***

By definition, all the studies included surgery as the main initial treatment combined with different adjuvant treatments. Overall, three categories of comparison of treatment strategies were reported in the 29 economic studies. The first category included the comparison of 'surgery alone' against 'surgery combined with different adjuvant therapies', such as CTx, RTx, or ETx (n=11) (161,166,167,240-244,247,250,251). The second category included the comparison of 'surgery, CTx, and trastuzumab' against 'surgery and CTx' (n=15) (164,165,168,170,235,239,245,246,248,252-257). The final category included the comparison of 'surgery and adjuvant CTx and ETx' against 'surgery and either CTx or ETx' (n=3) (162,163,238) (Table 3.2.).

***Type of economic evaluation***

The type of economic evaluation most frequently reported in these 29 studies was CUA (n=26) (161-168,170,235,238-248,251-255), of which eight studies included both CUA and CEA (164,170,245,247,251,253-255), and three studies included only CEA (n=3) (250,256,257) (Table 3.2.).

***Outcome measures of economic evaluation***

The majority of the included studies used QALY as the primary outcome measure (n=26) (161-168,170,235,238-248,251-255). Eight studies considered both QALY and LYG (164,170,245,247,251,253-255). Three studies used only LYG as the primary outcome measure (n=3) (250,256,257) (Table 3.2.).

***Economic outcome of economic evaluation***

The economic outcome most commonly reported in the economic evaluations included was ICUR (n=26) (161-168,170,235,238-248,251-255). Eight studies included both ICUR and ICER (n=8) (164,170,245,247,251,253-255). Three studies considered only ICER (n=3) (250,256,257) (Table 3.2.).

**Table 3.2 Characteristics of included economic evaluations**

| Author, year<br>Country<br>Type of economic study | Perspective<br>Type of economic model<br>Age of patients | Type of strategy | Benefit measures<br>Benefits/costs combination |
|---|---|---|---|
| Buendia, 2013<br>Colombia<br>CUA, CEA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Bai, 2012<br>China<br>CUA | Societal<br>Markov model<br>52 years | Surgery+ RTx vs. surgery | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Campbell, 2011<br>UK<br>CUA | Health care provider<br>Markov model<br>40 years | Surgery+ CTx vs. surgery<br>Surgey + CTx vs. surgery + CTx | QALY<br>Cost/ QALY |
| Hall, 2011<br>UK<br>CUA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY<br>Cost/ QALY |
| Purmonen, 2011<br>Finland<br>CUA | Societal<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY<br>Cost/ QALY |
| Yang, JJ, 2010<br>Korea<br>CEA | Societal<br>Not stated<br><39, 40-49, >=50 years | Surgery+ ETx vs. surgery | LYG<br>Cost/ LYG |
| Chen, 2009<br>China<br>CUA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Naeim, 2005<br>USA<br>CUA | Not stated<br>Not stated<br>65, 75, >85 years | Surgery+ ETx+ CTx vs. surgery+ CTx | QALY<br>Cost/ QALY |
| Dedes, 2007<br>Switzerland<br>CEA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | LYG<br>Cost/ LYG |
| Shiroiwa, 2008<br>Japan<br>CEA | Health care provider<br>Markov model<br>49 years | Surgery+ CTx+Trz vs. surgery + CTx | LYG<br>Cost/ LYG |
| Norum, 2007<br>Norway<br>CEA | Societal<br>Not stated<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | LYG, QALY<br>Cost/ LYG |
| Naeim, 2005<br>USA<br>CUA | Not stated<br>Not stated<br>65, 75, and 85 years | Surgery+ ETx+ CTx vs. surgery+ ETx vs. surgery+CTx | QALY<br>Cost/ QALY |
| Lievens, 2005<br>Belgium<br>CUA, CEA | Societal<br>Markov model<br>Not stated | Surgery+ RTx vs. surgery | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Karnon, 2002<br>UK<br>CUA | Health care provider<br>DES<br><65 years | Surgery+ ETx+ CTx vs. surgery+ ETx | QALY<br>Cost/ QALY |
| Hayman, 1998<br>USA<br>CUA | Societal<br>Markov model<br>60 years | Surgery+ RTx vs. surgery | QALY<br>Cost/ QALY, cost/ LYG |
| Desch, 1993<br>USA<br>CUA | Societal<br>Markov model<br>60-80 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |
| Hillner, 1993<br>USA<br>CUA | Societal<br>Markov model<br>60 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |

**(Continue Table 3.2.)**

| Author, year<br>Country<br>Type of economic study | Perspective<br>Type of economic model<br>Age of patients | Type of strategy | Benefit measures<br>Benefits/costs combination |
|---|---|---|---|
| Hillner, 1993<br>USA<br>CUA | Societal<br>Markov model<br>60 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |
| Hillner, 1992<br>USA<br>CUA | Not stated<br>Markov model<br>60 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |
| Hillner, 1992<br>USA<br>CUA | Not stated<br>Markov model<br>60 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |
| Hillner, 1991<br>USA<br>CUA | Not stated<br>Markov model<br>60 years | Surgery+ CTx vs. surgery | QALY<br>Cost/ QALY |
| Skedgel, 2009<br>Canada<br>CUA | Direct payer<br>Markov model<br>49 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY<br>Cost/ QALY |
| Vlaenderen, 2009<br>Belgium<br>CUA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY<br>Cost/ QALY |
| Kurian, 2007<br>USA<br>CUA | Societal<br>Markov model<br>49 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY<br>Cost/ QALY |
| Liberato, 2007<br>USA and Italy<br>CUA, CEA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Garrison, 2007<br>USA<br>CUA | Societal, and payer<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Millar, 2007<br>Australia<br>CUA, CEA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |
| Skedgel, 2013<br>Canada<br>CUA | Direct payer<br>Markov model<br>40, 50, 60, and 70 years | Surgery+ CTx+Trz vs. surgery + CTx vs. surgery | QALY<br>Cost/ QALY |
| Hedden, 2012<br>Canada<br>CUA, CEA | Health care provider<br>Markov model<br>50 years | Surgery+ CTx+Trz vs. surgery + CTx | QALY, LYG<br>Cost/ QALY, cost/ LYG |

(Note) CTx: chemotherapy; RTx: radiotherapy; ETx: endocrine therapy; Trz: trastuzumab; CUA: cost-utility analysis; CEA: cost-effectiveness analysis; QALY: quality adjusted life year; LYG: life year gained; ICUR: incremental cost-utility ratio; ICER: incremental cost-effectiveness ratio; Adj: adjuvant; DES: discrete event simulation; USA: United States; UK: United Kingdom , *Different entry age into the model.

***Time horizon of economic evaluation***

Of the 29 studies, 24 studies mentioned the time horizon for economic models, and the duration of time horizon ranged for 10 years (n=2) (167,250), 15 years (n=2) (170,256), 20 years (n=1) (247) , 25 years (n=1) (168), 28 years (n=1) (245), and lifetime horizon (n=17) (161,164-166,239-244,246,248,251,252,254,255,257) (Appendix 9.).

***Types of model used in economic evaluations***

Except for four studies (162,163,250,253), all other included studies (n=25) reported the type of the economic model, including Markov model (n=24) (161,164-168,170,235,239-248,251,252,254-257), and discrete event simulation (DES) (n=1) (238) (Appendix 9.).

***Cycle length for the Markov model***

Except for three studies which did not mention their model cycle length (166,239,241), the cycle length in other 21 studies using Markov model varied as 1 year (n=11) (161,164,167,240,242-244,248,254-256), 1 month (n=6) (168,235,246,251,252,257), 3 months (n=3) (165,170,245), and 6 months (n=1) (247) (Appendix 9.).

***Disease states and pathways***

Except for two studies (162,163), all other 27 included studies reported the transition states. The most common of these 27 were the disease-related states, i.e. disease-free (state where patients are free of cancer after successful surgical treatment), recurrence (state where the cancer came back after successful surgical treatment), and death states. Two studies considered contralateral tumour (i.e. tumour in the opposite breast) as a transition state (161,250). Only 13 studies reported treatment-related states including trastuzumab cardio-toxicity state, i.e. heart failure (n=7)

(165,235,245,248,253-255), and CTx-related toxicity state, i.e. nausea, vomiting, and febrile neutropenia (n=6) (166,240-244) (Appendix 9.).

***Sensitivity analysis***

Of the 29 studies, only one did not conduct sensitivity analysis (241), and two studies did not report the type of sensitivity analysis (242,244).

The number of sensitivity analysis types reported in the 26 studies ranged from one (n=10), two (n=12), to three types of sensitivity analysis (n=4), and the types of sensitivity analysis included one-way (n=20), multi-way (n=4), probabilistic (n=13), threshold (n=3), analysis of extreme (n=2), and scenario sensitivity analysis (n=4).

Except for one, all studies reported the area of uncertainty tested. Most studies assessed uncertainty around utility, cost, treatment effect, transition probabilities, duration of treatment benefit, and discount rate. Only one study assessed the uncertainty around the age (164), and one study assessed uncertainty around tumour biology (244). Fourteen studies reported the information sources used for defining uncertainty ranges in sensitivity analysis, including literature (n=8) (161,168,170,235,238,245,248,251), assumption (n=5) (162,246,250,253,256), and expert opinion (n=1) (165) (Appendix 9.).

Amongst the 26 studies which conducted deterministic sensitivity analyses, discount rate (n=13) (162,163,165,168,169,239,245,252-257) and treatment duration benefit of either CTx (n=5) (161,240,242-244) or Trz (n=5) (164,165,168,254,257) were the major key parameters influencing the ICER results, followed by initial costs of treatment of trastuzumab (n=8) (164,165,168,169,239,252,253,256), RTx (n=1) (167), and age at diagnosis (n=2) (170,251).

***Presentation of economic results***

Only 11 studies presented both aggregate and disaggregate results of ICER (161,165,167,169,170,238,247,251,252,254,255) (Appendix 9.). Twenty-three studies presented deterministic results (deterministic models) (161-164,166,167,169,239-247,250,251,253-257); of which only one study presented both deterministic and probabilistic results (169), and the results of both base case and PSA were quite similar (169) (Appendix 9.). Six studies presented only probabilistic studies (probabilistic model) (165,168,170,238,248,252).

### 3.4.3. Resource use, costs, and benefit measurement

***Types of resource use and costs included in the economic evaluation studies***

The majority of the studies included only direct medical cost (n=19) (161-165,170,238,240-245,248,252,254-257), six studies included direct medical cost and direct non-medical cost (167,168,239,246,247,251), three studies included direct medical and non-medical costs, and indirect cost (166,250,253), and one study included direct medical and indirect costs (235) (Appendix 10.). Direct medical cost included drug or treatment strategy costs (n=31), drug administration (n=14), screening test (n=6), treatments for adverse events (n=20), recurrence cost (n=19), doctors' visits (n=16), hospitalisation (n=14), monitoring tests (n=16), mammogram surveillance (n=3), screening for adverse event (CHF, sonography) (n=7), terminal care (n=5), staff cost (n=5), follow-up scan for metastasis (bone and liver scan) (n=1). Direct non-medical cost included travel costs (n=5) and out of pocket costs (n=1), while indirect costs included loss of productively (n=4).

***Unit costs and resource use source***

Except for two studies (247,255), all the other included studies reported the information sources from which the unit costs were derived, including National statistics (n=15),

literature (n=12), estimation based on expert opinions (n=8), or specific hospital financial department (n=2) (Appendix 10.).

Except for seven studies (164,166,243,246,252,254,257), all the other included studies reported the information sources from which the resource-use were derived, including guidelines (n=6), hospital database (n=7), alongside clinical trial (n=6), expert panel (n=6), published literature (n=6), clinical practice (n=4), retrospective medical records (n=2), and assumption (n=1).

***Utility valuation methods, measurements, and sources***

Amongst the 26 studies which conducted CUA, only three studies directly reported the methods, instruments, and respondents used to generate the utility values (161,165,252). The methods, instruments, and respondents used to calculate utility values were retrieved from references cited in the other 23 included studies. Although references have been retrieved, still 11 studies did not report the utility instrument (162-164,166,240-245,254), 4 studies did not report the respondents (162,166,254), and 10 studies did not report the method of valuation (162,163,166,240-244,253,254). Overall, direct elicitation was the most common utility measurement (n=9), followed by EQ-5D (n=5), SF-6D (n=2). Time trade-off (TTO) was the most commonly used valuation method (n=10), followed by standard gamble (SG) (n=10), and visual analogue scale (VAS) (n=4). Health care professionals was the most commonly used type of respondents to elicit utility values (n=13), followed by patients (n=9) and population (n=3). Except for three studies (163,166,244), the other included studies reported the source from which the utility values were retrieved, including published literature (n=14), systematic review of literature (n=4), expert opinions (n=4), and estimation (n=1) (Appendix 10.).

### *Discounting rate of costs and outcomes*

All studies reported discount rates for costs. The most common discount rate for costs was 3% (n=17), followed by 5% (n=9), 3.5% (n=2), and 6% (n=1). Except for one study (255), all other included studies reported discount rates for outcomes and the most common discount rate for outcomes was 3% (n=19), followed by 5% (n=9), 3.5% (n=2), and 1.5% (n=2) (Appendix 10.).

### 3.4.4. Quality assessment of economic evaluations

Quality assessment was categorised into four categories, including model structure, data source, uncertainty, and result presentation and interpretation.

#### 3.4.4.1. Model structure

All included studies described the model structures, but did not provide good justifications for these model structures. None of the 29 economic studies met all the 'model structure' criteria in the economic checklists (questions 1-23)

***The importance of the economic research question***

Except for nine studies (163,164,166,241,243,244,253-255), all the other 20 included studies addressed a clear research question specifying study population, interventions, comparator, and outcomes (question 1). Except for five studies (166,241,242,244,250), all the other 24 studies clearly stated the importance of the economic research question (question 2). Only one study provided a justification for why a modelling approach was required (253) (question 3) (Appendix 11.).

***Target population, subgroup analysis, location, and perspective***

Except for one study (169), all other 28 studies described the characteristic of the target or base-case population in terms of their age, sex, and condition (question 4). Although eight studies conducted subgroup analysis (161-163,166,241,248,250,251), none of these studies provides evidence to support the assumption behind the subgroup differences (question 5). Only one study provided the setting of health care (question 6), i.e. primary or secondary (247). Except for five studies (162,163,242-244), all other 24 included studies reported the country or location from where the studies' perspectives were taken (question 7). Amongst the 24 studies that mentioned their perspectives, none of the studies gave a justification of the choice of perspectives (question 8) (Appendix 11.).

***Economic model scope***

The costs included in 16 studies were consistent with the perspective chosen for the economic evaluation (question 9) (164,165,167-170,238,245,246,248,250,253-257). Only four studies clearly stated the scope of the model, including the perspective chosen, the population analysed in the model, the interventions and comparators, and time horizon of the model (question 10) (161,235,251,253). Only one study justified the choice of the comparator (253) (question 11), and only four studies provided details about the alternative treatment being compared (question 12) (235,240,246,253).

***The choice of type of economic evaluation***

Of the 27 studies which reported the types of economic evaluation (161-163,165-168,170,235,238-241,243-248,250-257), only four studies justified the choice of a certain type of economic evaluation (167,238,239,257); of which one study stated that CUA was not conducted due to the lack of utility data (257). In contrast, the other three studies stated that they conducted a CUA to assess the impact of breast cancer on quality of life (167,238,239) (questions 13 and 14)

***The choice of model structure***

The model structures (disease states or pathways) were consistent with the treatment pathways of the disease in four studies by using treatment pathway guidelines as the source of data to build the model structure (165,167,250,257) (questions 15 and 16). Except for two studies (245,253), all other 27 included studies clearly described the structural assumptions, i.e. assumptions related to the model structure, or modelled population, that were made in the model. Of these 27 studies, only seven studies provide justifications for choosing these structural assumptions (162,167,235,238,243,251,256) (question 17) (Appendix 11.).

Only six studies provided the rationale for the model structure (235,238,240-243) (question 18). The reasons for choosing a Markov model were to model disease with a long time frame and recurrent events (n=5) (165,240-243), while the reason for choosing DES was to model patients' treatment history (n=1) (238). Except for seven studies, the other 22 included studies provided a diagram for the model (162,163,166,167,248,253,256) (question 19).

***The choice of lifetime horizon***

Except for 10 studies (161-163,167,170,238,247,250,253,254), the other 19 studies used lifetime horizon. Of the 10 studies that didn't use lifetime horizon (161-163,167,170,238,247,250,253,254), only one study justified the choice of short time horizon, i.e. non-lifetime horizon due to the lack of follow-up data (167) (questions 20 and 21). Of the 21 studies which defined the cycle length (161,164,165,167,168,170,235,240,242-248,251,252,254-257), none of the studies provided clear justification for choosing the cycle length (question 23).

#### 3.4.4.2. Data source and cost

Generally, information about the quality of studies from which the included economic studies appeared to be poor at providing information about the quality of studies from which the effectiveness data were derived, which impedes the validity and robustness of the economic evaluations.

***Effectiveness data source***

None of the 29 economic studies met all the criteria for 'data source' in the economic checklists (questions 24-57). Except for two studies (240,241), the other 27 economic studies stated their effectiveness source, of which, only three studies derived the effectiveness data from a single study (167,250,252). Of the 27 studies one study provided details of the design of the effectiveness study (250), and one study provided

details about the synthesis of the previous studies (255). Of the 27 economic studies which stated their effectiveness sources, only nine studies justified the rationale behind choosing the source of effectiveness data (163,165,167,168,238,247,250,251,253), and only three studies assessed the quality of the data used as a source of effectiveness (167,238,250). None of the 27 studies used expert opinion as a source for effectiveness data (questions 24-30) (Appendix 11.).

***Data source and assumptions for transition probabilities and treatment effects***

Except for seven studies (163,239,240,242,243,253,256), all the other 22 included studies described the data used to derive the baseline probabilities for patients' outcomes, (i.e. recurrence, death) but only three of the 22 studies justified the rationale behind choosing these data (165,167,250) (question 31). Of the 23 studies that used state-transition models (Markov model), none of the studies provided details on how the transition probabilities were calculated and only one study included half-cycle correction to adjust for the transition between the cycles (165) (questions 32 and 33). Eleven studies used meta-analysis to derive treatment effects (161-163,170,235,238,239,241,246,247,251) (question 34). Only sex studies described the methods to extrapolate short-term outcomes to long-term outcomes, i.e. survival models (161,235,239,248,251,252) (questions 35 and 36). Except for nine studies (162,163,166,167,238,245,247,250,253), the other 20 included studies described the assumption regarding the continuing effect of treatment once the treatment had been stopped, of which 14 studies justified the assumption behind the continuing effect of treatment (164,165,168,170,235,240-244,246,252,256,257) (questions 37 and 38).

***Data incorporation in the model***

Eighteen studies clearly described the method of data incorporation in the model as a point estimate (n=6) (165,166,239,243,255,256) or distribution (n=12) (161,168,170,235,238,245,246,248,251,252,254,257) (question 40). None of the

twelve studies, which incorporated data as a distribution, justified the choice of distribution for the model parameters. Moreover, none of the six studies, which incorporated data as a point estimate, justified the choice of ranges for the model parameters (question 41).

***Source of utility values***

Only four studies used utility data derived from a population different from their study population (162,247,251,252) (question 39). Six studies clearly reported the method used to value the health utilities (i.e. TTO, SG, or VAS) (161,165,167,169,245,252), and eight studies clearly provided details of the respondents from whom the health utility values evaluations were obtained (161,165,167,240,243,244,247,252); only four studies clearly reported the type of utility-based measures used to derive the utility value, i.e. EQ-5D, SF-6D, or direct elicitation (161,165,247,252) (questions 42-44).

***Resource use and unit costs***

Four studies reported the resource and their unit cost separately (161,164,170,253) (question 45). Except for three studies (164,166,251,254), all other 26 studies reported the methods for the estimation of the resource quantities and their unit costs (question 46). Except for four studies (241,242,244,248), all the other 25 studies included reported the cost currency; of which three studies did not mention the year from which the costs were derived (170,255,257). Three studies adjusted the prices for inflation (170,255,257), and four studies adjusted the price for currency conversion (168,246,253,257) (questions 47-49). All the 29 included studies reported discount rate(s) for costs and outcomes, of which only one study did not discount the outcome (255), and only four studies justified the discount rate that was chosen for both costs and outcomes (170,239,252,253) (questions 49-52).

***Choice of outcome measures***

The majority of the included studies clearly reported the primary outcome measure (n=25) (161,163,165-170,238-241,243-248,251-257); of which only three studies justified the rationale behind choosing this outcome measure (165,239,252) (question 53).

***Reporting of study parameters***

Except for nine studies (162,163,238,240-244,255), the other 20 included studies reported the values for their study parameter, including costs, outcomes, and utilities. Fourteen studies provided the ranges that reflected the uncertainty around study parameters (161,165,166,168,169,239,245,246,248,250-252,254,255). Except for nine studies (162,163,238,240-244,253), the other 20 included studies reported the references of choosing certain parameters (questions 54-57).

#### 3.4.4.3. Uncertainty of the model results

Generally, the included studies were poor in describing all types of uncertainty of models. None of the 29 economic studies met all the criteria for 'uncertainty' in the economic checklists (i.e. met criteria 58-70) (Appendix 11.).

***Characterising uncertainty***

Amongst the 28 studies which conducted deterministic sensitivity analysis, 9 studies presented the results in a Tornado diagram (165,167,169,239,250,251,253,255,257). None of the studies presented all the types of uncertainty. Nineteen studies addressed methodological uncertainty, which is the uncertainty related to the method used to value and measure costs and health outcomes such as discount rate through the use of one-way sensitivity analysis (162-165,168,169,239,243,245,247,250-257).

Nine studies considered heterogeneity between individuals in the model cohort by analysing different age subgroups (161,162,164,166,170,246,248,250,251). However, only 13 studies considered PSA to address parameter uncertainty. Amongst the 13 studies (161,165,168-170,238,245,246,248,251,252,254,257) that conducted PSA, 10 studies presented the results in CEAC and CE plan (161,168,238,245,246,248,251,252,254,257) (questions 58-68).

#### 3.4.4.4. Result presentation and interpretation

Generally, the included studies were good in presenting and interpreting their results. None of the 29 economic studies met all the criteria for 'Result presentation and interpretation' in the economic checklists (met criteria 71-79).

All the 29 included studies reported the ICER results, and only 11 studies reported the ICER results separately from the costs and benefits of each intervention (reported both aggregated and disaggregated results) (161,165,167,169,170,238,247,251,252,254,255). Fourteen studies compared their findings with the previous literature.(163,165,167,168,239,247,248,251,252,254-257). Sixteen studies summarised their key findings in the discussion part and how they fitted with their conclusion (161,164,166-170,239,245,248,250-252,254-256). The four studies which assessed the issue of generalisability (161,168,246,254) declared their results were not generalisable to the population of the clinical practice. Moreover, 18 studies discussed the limitations of their study design and analysis (161-164,167-170,238,239,245,247,248,250,251,254-257) (questions 71-79) (Appendix 11.).

### 3.4.5. Types of disease and treatment-related health states identified from the 29 economic evaluation studies

Types of health states of different treatment strategies for women with primary breast cancer reported in the 29 included studies were stratified by their age group and treatment strategies (Appendix 12.).

#### 3.4.5.1. Disease-related health states

Of the 29 studies, two economic studies included only women over 70 years old; these two studies did not report the types of economic models and the transition states used (162,163). Three economic studies conducted subgroup analysis for older women aged over 65 years by using similar economic models and transition states as in younger women between 50 and 65 years old (166,246,248) (Appendix 12.).

In the other 27 studies assessing the breast cancer treatment strategies in both patients younger and older than 65 years, the main disease-related health states considered in the models were DF, recurrence, and death. However, the terminologies used to define the DF health states varied, i.e. different terminologies were used in the DF state in different models, namely well, relapse free (RF), and complete response (Appendix 12.).

After receiving surgical treatment, patients remained DF until they experienced local recurrence, regional recurrence, distant recurrence (DR), or contralateral tumour. Patients who experienced local recurrence, may become DF again or experience a second local recurrence or DR. All the 27 studies, which reported the health states considered a breast cancer recurrence state. However, these studies defined recurrence states differently. Fourteen studies explicitly separated different types of recurrence into different heath states, including locoregional recurrence (LRR), DR (n=13) (161,167,168,170,238,245,246,248,250,251,254,255,257), or local recurrence

(LR), regional recurrence (RR), and DR (n=1) (256). Ten studies combined LRR and DR within the same state (n=10) (164-166,240-244,247), but the main reason behind combining some types of recurrence in the same health state was not justified. In addition, of the three studies that omitted the LR (239,252,253), two studies justified this omission as being due to lack of data (239,252) (Appendix 12.).

Except for seven studies (161,165,168,246,250,254,255), all the other 20 studies didn't consider contralateral breast cancer (CBC). In addition, the seven studies that did consider CBC handled the contralateral tumour differently; only two studies explicitly defined CBC as a separate health state (161,250). Although five studies considered CBC within the same recurrence state alongside other recurrence types, including local, regional, and DR (165,168,246,254,255); no justification was provided behind considering CBC as one type of recurrence.

Of the 27 studies, seven studies considered that patients returned DF state after LR state with no justification provided (165,168,240-244); and only seven assumed that the second local recurrence is DR (164,165,168,238,246,255) .

#### 3.4.5.2. Treatment-related health states

Treatment-related health states were categorised into three treatment strategy groups, 'surgery plus adjuvant therapy vs. surgery' (n=11), 'surgery plus CTx plus trastuzumab against surgery plus CTx' (n=15), and 'surgery plus ETx plus CTx vs. surgery plus ETx or CTx' (n=1), since they included drug-related side effects that are specific to those treatment categories.

***Surgery plus adjuvant therapy vs. surgery (n=11)***

The main adverse events considered in the models were endometrial cancer, thromboembolic, and pulmonary disease associated with adjuvant ETx; nausea, vomiting, and febrile neutropenia associated with adjuvant CTx; skin irritation, discomfort, fatigue, pneumonitis, cardiac toxicity, and secondary malignancy associated with adjuvant RTx. However, these studies dealt with these adverse events differently. Of the seven studies which included adjuvant CTx as the comparator arm, six studies modelled the adverse effects of CTx as separate health states (n=6) (240-244), and only one study considered the impact of adverse effects of CTx on cost and utility (161). Of the three studies which included RTx in the comparator arm (167,247,251), one study did not consider nor modelled the impact of adverse events (251); the other two studies considered the impact of adverse events on costs. The study that included adjuvant ETx in the comparator arm considered the impact of adverse effects of ETx and RTx on the cost (250) (Appendix 12.).

***Surgery plus CTx plus trastuzumab against surgery plus CTx (n=15)***

Cardiotoxicity was the main adverse event considered in studies that evaluated adjuvant trastuzumab. Six studies modelled adverse effects of trastuzumab (n=6) (165,169,245,248,254,255) as separate health states, but the rationale behind separating these adverse events into a different health states was not described. Eight studies considered the impact of the adverse events on costs, QoL, or both (164,168-170,239,246,253,256,257). One study did not consider the impact of adverse events in the model (252) (Appendix 12.).

***Surgery plus ETx plus CTx vs. surgery plus ETx or CTx (n=1)***

None of the studies reported adverse events as separate health states. Only one study considered the impact of adverse events of CTx and ETx on cost and QoL (238).

### 3.4.6. Variation in cost-effectiveness results across different age groups

Among the eight studies which analysed the cost-effectiveness results in older women (162-164,166,170,246,248,250), seven studies reported the results across different age groups (Appendix 13.) (162-164,166,170,248,250)and one study did not report the cost-effectiveness result (246). Desch *et. al.* (1993) showed that the benefit of adjuvant CTx declined with age; the QALYs gained from the addition of adjuvant CTx decreased from 2.8 months for a 60 years old woman to 1.4 months by age 80 with a less favourable incremental cost-effectiveness ratio of $28,200/ QALY, $31,300/ QALY, $36,300/ QALY, $44,400/ QALY, and $57,100/ QALY for older women aged 60, 65, 70, 75, and 80 years old, respectively (166).

Two studies by Naeim *et. al.* (2005) reported that cost-effectiveness results for older women with different ER and nodal status across different age groups (162,163). For older women aged 65 years old with node (−) ER (+) status, adjuvant ETx was more cost-effective ($10,194/ QALY) than CMF or AC CTx. Adding CTx to ETx is still cost-effective as compared to CTx alone but are associated with less favourable cost-effectiveness ratio of $22,220/ QALY when it was added to ETx. Similarly, In a 65 year old woman with node (+) ER (+) disease, ETx was more cost-effective with $6,520/QALY than CMF or AC chemotherapy. Adding adjuvant ETx gives the incremental cost-effectiveness ratio of $12,890/QALY, thus, for patients aged 65 or 75 years old with ER (+) and either positive or negative node status would be given adjuvant ETx. Once all women received adjuvant ETx, then combined therapy with AC could be considered. However, in patients who were ER (−), ETx does not work, and thus CMF was cost-effective ($30,451/ QALY) as compared to no treatment and $46,572/ QALY for AC compared to CMF (163). In a 75 years old with node (−) disease ER (+) disease, adjuvant ETx was cost-effective ($19,530/ QALY) as compared against other treatments. Adding adjuvant CTx was associated with less favourable cost-effectiveness results $280,000/QALY as compared to patients aged 65 years old

since the effect of adding CTx declined with age, and thus the QALY gained were much smaller and. In a patient who is ER (−), CMF was more cost-effective $75,559/QALY as compared to no adjuvant treatment (163),

In Yang *et.al*. (2010), except for patients aged over 50 years old, the cost-effectiveness ratio of using adjuvant tamoxifen become less favourable with older age.
With an ICER of $1137/ LYG, $1895/ LYG, $739/ LYG for age group of <39, 40-49, and >50 years old (250).

Several studies showed that using adjuvant trastzumab in addition to surgery and adjuvant CTx become less favourable with older age, with ICER of $18,970/ QALY, $60,000/QALY, and $150,000/ QALY for age over 50, 75, and 79 years, respectively (170). In addition, in Millar, *et.al*. (2010) study the ICER increased from $22,793/ QALY in patients aged 50 years to $27,734/ QALY in patients aged over 65 years (164). Furthermore, in Van Vlaenderen, *et. al*. (2009) study, the ICER increased from €6,478/ QALY, €8,131/ QALY, €11,868/ QALY, €25,755/ QALY, and €100,356/ QALY, for the age group <50, 50-59, 60-69, 70-79, and >80 years old (248).

## 3.5. Discussion

### 3.5.1. Main finding

This systematic review provides a methodological critique of the model-based economic evaluations comparing the cost-effectiveness of different strategies for adjuvant treatment in postmenopausal women. The disease and treatment related-states associated with the surgical treatment strategies identified from this review for postmenopausal women were used to inform the design of disease health states associated with surgical treatment strategy for older women with primary breast cancer.

Around half of the studies separated LRR and DR into two separate health states, whilst a few studies considered CBC as a separate health state without giving any justification; a few studies defined the second and third recurrence of breast cancer as metastasis in the models without giving any justification. The majority of the studies did not separate the impact of adverse events of treatments into separate health states.

The majority of the included economic studies used a Markov model with lifetime horizon and 1-year cycle length. None of the studies which included only older women over 65 years reported the economic models and transition states used in the models. A few studies reported subgroup analysis for older women over 65 years old. However, economic models and transition states were used for both patients younger and older than 65 years old. In general, the studies included in this review appeared to be poor in providing justifications behind the choice of model structures and data sources.

The variations in intervention, comparator arm, resource use, cost, and utility measurement make the comparison between the studies unfeasible, and have contributed to the overall lack of consensus on assessing the cost-effectiveness in postmenopausal women with primary breast cancer. Moreover, the results from these

studies could not be generalised with respect to older women since these studies did not specifically include older women with primary breast cancer.

### 3.5.2. Disease-related health states for the surgical pathways in older women with primary breast cancer

Based on the main findings of this systematic review, disease-related health states associated with the surgical pathways as an initial treatment in older women with primary breast cancer were designed based on the following assumptions.

#### 3.5.2.1. Assumption one: health states are applicable across age groups

Of the previously published systematic reviews that assessed the efficacy and safety for using different adjuvant treatments in postmenopausal women with primary breast cancer, only one systematic review assessed the efficacy and safety of using different treatment strategies particularly in older women (89,181,258-261). These systematic reviews showed that similar outcome measures were used to assess the efficacy of surgery as the main initial treatment in both patients younger and older than 70 years, including recurrence and death (89,181,258-261).

In the current systematic review of economic evaluations, similar health states associated with postmenopausal women were applied for patients with a subgroup over 65 years old. Moreover, the outcome measures identified from the previous cohort study of older women over 70 years old matched well with the outcome measures identified from these systematic reviews of postmenopausal women. Therefore, it was assumed that the types of models and disease transition states used for patients younger than 65 years old in the literature are applicable to older women over 65 years old.

#### 3.5.2.2. Assumption two: the surgical treatment model is transferable

As patients who received surgical treatment have similar outcome measures in both postmenopausal women and women over 70 years old, and hence, it was also assumed that the types of model and disease transition state used for modelling the cost-effectiveness of surgery as the initial treatment in literature can be directly used to model the surgical pathway for treating older women with primary breast cancer.

***Disease-related transition states***

Although the main transition states considered in the surgery pathway were DF, recurrence, and death, several assumptions were made on the recurrence states to incorporate the disease-related health states in the model design since there were a variety of definitions for the recurrence states identified from this current systematic review.

The way that some of the included studies defined the transition states was inconsistent with ISPOR Task Force on Good research Practices on Modelling Studies. The ISPOR Task Force (262) recommended that health states which reflect a similar clinical course of the disease (e.g., similar treatment, outcomes) should be combined in one health state (263). According to the European Society for Medical Oncology (ESMO) guideline, patients with either LR or RR undergo the same treatments (109). However, there is no data showing any difference in the disease progression associated with both types of recurrence. Therefore, the assumption was made that treatment pathways and disease progression for patients with RR are similar to those with LR. Thus, LR and RR can be combined in the same health state.

Metastasis is considered to be a systematic disease. Comparing with LR and RR, metastatic recurrence is generally not curable (264). The aim of treating metastatic disease is to improve patients' quality of life and prolong patients' survival rather than

cure the disease (109). The role of local therapy such as surgery and RTx is limited in managing metastasis, and the main treatment used for managing metastasis is systematic therapy such as ETx, CTx, and sometimes trastuzumab (264). Therefore, the clinical course and treatment pathways for metastasis are different from local or regional recurrence, and thus, it was assumed that recurrence due to metastases should be regarded as a separate health state.

The American Cancer Society considers CBC as a new tumour rather than a recurrence, and hence, it is not a consequence of the initial treatment (265). However, clinical guidelines did not provide any detail about how CBC is treated (36,109,265). NICE Guidelines on early and locally advanced breast cancer reported that the risk of acquiring CBC in patients with primary breast cancer is less than 0.3% per annum (36), and therefore, CBC was not considered in the design of the model since the incidence of CBC is low, and an assumption was made to omit CBC.

A few studies included in the systematic review assumed that a second LR is a DR. Since the LR is curative (109), there is a chance that patients may get a second local recurrence after they were cured from the first local recurrence of breast cancer. Therefore, it is not appropriate to assume that a second local recurrence is equal to a DR, and thus, the second local recurrence was treated the same as another LR following the first recurrence.

***Treatment-related transition states***

The majority of the economic studies that included adjuvant trastuzumab and adjuvant ETx in their treatment strategies considered the impact of the toxicities of treatment on costs and QoL; whilst the majority of the studies that included adjuvant CTx in their treatment strategies considered CTx toxicities as one of the transition states in

modelling the cost-effectiveness of adjuvant CTx. None of the studies considered the impact of surgery complications on the cost and QoL.

According to the ISPOR good practice guideline on modelling studies, adding a large number of transitions states may complicate the model and make it more difficult to manipulate, and thus, it is difficult to include all the side effects as separate transition states (266). Therefore, considering only the impact of adverse events of treatments may be more appropriate. An assumption was made to consider the impact of surgical complications and side effects of endocrine, with the highest prevalence, on the cost and quality of life, i.e. the resource use and utility information should include the impacts of the side effects.

**Cycle length**

Since PETx aims to control the disease progression rather than cure the cancer (44), time to local disease progression in case of PETx is much shorter than that of surgical therapy, and therefore the time to event (time to disease progression) were assumed to be different between both strategies (181). The ISPOR guideline for economic modelling recommended to choose a cycle length in Markov models in which multiple changes in disease events or costs are unlikely to occur during one cycle (263), and therefore, the cycle length was assumed to represent the shortest time to an event, which in this case is the time to disease progression in patients receiving PETx. None of the economic studies included in this systematic review reported cycle length for the PETx pathway. Patient-level data, such as observational studies which considered PETx as the main initial treatment, were used to obtain the time to disease progression (Chapter 2.).

**Life time horizon and discounting**

The majority of the studies used lifetime horizon. As stated by the ISPOR guideline, lifetime horizon is the most appropriate horizon to reflect differences in the long-term outcome of different strategies, such as survival (266), and therefore, lifetime horizon was adopted in the model for this research (Chapter 4).

Discounting of the costs and the outcomes is required if the time horizon is longer than one year (267). According to the NICE guideline (268), a discounting rate of 3.5% of both the costs and outcomes is required in a model used to analyse lifetime horizon for chronic disease, such as breast cancer (268). Therefore, a discount rate of 3.5% for both costs and outcomes was used in this research project (Chapter 4).

### 3.5.3. Benefits and outcome measures

Generally, effectiveness or efficacy data, i.e. event probabilities and treatment effects are obtained from high quality studies such as clinical trials (160,237). Although the majority of the included studies in this systematic review derived the event probabilities and treatment effect from RCTs, none of these RCTs were specifically conducted in older women with primary breast cancer, and thus, are not applicable to the study population of this research project. As there is no large-scale well-designed RCT conducted in older women with primary breast cancer due to poor recruitment (143), alternatively, observational studies with long follow-up and large sample size was used in this research to derive transition probabilities and times to events (Chapter 2.).

Overall, the included studies were poor in reporting the methods used to measure and estimate utility values. Only three studies provided details of the utility measurements, type and age of respondents (161,165,252). All three studies derived their utility using the EQ-5D instrument, of which two studies were based on UK breast cancer patients (161,252), and one based on Swedish breast cancer patients (165). However, the age

of respondents limited the usefulness of applying these utilities to the older women with breast cancer, since they were not specifically conducted in older women with primary breast cancer. Alternatively, other sources were used to obtain utility values (Chapter 4).

### 3.5.4. Resource use and costs

The majority of the studies included in the systematic review were of good quality in reporting the method used to estimate resource and unit costs, because the majority of resource use and costs were measured using patient-level data or previous literature rather than being estimated by an expert panel. Although most studies included in the systematic review reported a detailed breakdown of type of costs included – such as treatment costs, recurrence costs, and follow-up costs – they are not applicable to this research project. First, the majority of the studies were conducted in countries other than the UK with different currency and methodology to estimate unit costs and resource use. Second, most studies did not report a comprehensive or detailed breakdown of resource use quantities and unit costs. Finally, the resource use that were quantified in the previous studies were associated with younger populations which may not reflect the actual resource consumption associated with older patients in this research.

### 3.5.5. Uncertainty

Ideally, an uncertainty analysis includes a series of deterministic (including one and two-way sensitivity analyses) and a stochastic analysis (including PSA). One and two-way sensitivity analyses provide some insight into the key parameters influencing the model results (211), and PSA has the advantages of exploring the joint uncertainty across all the parameters at the same time (173). A few studies included in the systematic review conducted both types of sensitivity analysis. Moreover, only a few

studies presented the probabilistic result, which is very important to examine the joint uncertainty around the ICER point estimate (173).

The majority of the studies included in the systematic review that examined the key factors influencing the ICER found that treatment duration benefit – i.e. the persistent effect of a treatment after that treatment has been stopped – and discount rates were the most common key parameters influencing the results. However, the treatment duration benefit was assessed in the studies which included adjuvant therapies such as CTx and BTx. Since PETx is prescribed for the lifetime for older women with primary breast cancer, treatment duration benefit was not assessed in this research.

### 3.5.6. Cost-effectiveness results across different age groups

Despite the results were from different countries with different treatment strategies, there was a trend toward less favourable cost-effectiveness results with older age. This could be explained by the following reasons: First, efficacy of some treatment decreases with increasing age, such as CTx (Section 1.3.4.3).

Second, there is a bias in LYG and QALYs measured in older women due to decrease life expectancy with time. Economic evaluation focuses on efficiency of resource allocation to maximize health gain (143). Health gain is measured in some way by life year gained, quality of life or combination of both (269). These measures may be biased against age as older people are expected to have a shorter life gain from certain health care interventions compared with younger (270). For example, if QALY is used as a measure of health gain, an economic evaluation will favour maximization of QALY gain therefore if two people that are similar in everything except age, the QALY gain from certain treatment will be smaller in older people than younger people because the years of life that older patients are expected to live as a result of treatment are less compared with younger patients (270). Therefore, economic evaluation may favour

allocation health care resources for younger people as they have a greater capacity to benefit from certain health care resources such as health care intervention.

Third, increasing the complications of surgery due to the higher prevalence of the comorbidities which resulted in prolonged hospitalisation, increasing hospital admission rate and thus, increase the costs of treating older women (Section 1.4.4.; Section 2.3.6.).

### 3.5.7. Strengths and limitations

This is the most updated systematic review of economic evaluations conducted to review and critique the modelling methodology in postmenopausal women with primary breast cancer, which could provide some insights into the key methodologies that are important to consider during designing an economic model for breast cancer. A wide range of databases was searched using varieties of keywords and MeSH terms that enhanced the coverage of the majority of the economic evaluations. In addition, two quality assessment checklists were used to critique the economic evaluations covering a wide range of critiquing questions that enhance the assessment of the studies' methodologies.

However, there are some limitations that apply to this systematic review. First, this review included only fully published economic studies in English language from 1996 until the present, which may incur language and reporting biases. Second, there is a probability of underestimating or overestimating the quality of those studies, as some of them may not clearly describe the study design, effectiveness data, cost data, type of analysis, model assumption, and other questions that CHEERS and Philips checklists want to assess.

## 3.6. Conclusion

This systematic review provides some insights to the design of a model to include disease-related health states associated with the surgical pathways in older women with primary breast cancer. However, given that none of the studies included in this systematic review considered PETx as one of the treatment strategies, the disease health states associated with using PETx in older women need to be derived from other sources (Chapter 4). The designed evidence-based economic model was populated by using a longitudinal data source (Chapter 2.) to derive transition probabilities and resource use, and also synthesis of data from different sources to derive utility values (Chapter 4).

# Chapter 4. An economic model comparing the cost-effectiveness of primary endocrine therapy against surgery as the initial treatment strategy for older women with primary breast cancer

## 4.1. Introduction

Breast cancer often has repeated clinical events (complications) that happened during a long follow-up period and have a detrimental impact on the patient's QoL and survival (Chapter 3.). It is also expected that treatments for breast cancer will influence utility and clinical effectiveness over patients' lifetime. Therefore, an economic model considering recurrent events for the lifetime horizon will be a good option to assess the cost-effectiveness of different breast cancer treatments.

A decision analytical model simulates the expected costs and outcomes either for a group of patients who share similar characteristics (in a cohort model, e.g., decision tree and Markov model) or for each patient individually (in a patient-level simulation model, e.g., discrete event simulation [DES]) (271).

However, a decision tree is not suitable to model chronic diseases such as breast cancer with recurrent events, as it requires to structure all the events, which repeatedly occur during the course of the disease in a decision tree, and consequently, the tree will become much too 'bushy' with too many branches, making it difficult to analyse (143,160). Alternatively, a Markov model can be used to stimulate the natural progression of chronic disease and used for diseases in which events occur repeatedly, such as cancer recurrence (160).

A Markov model includes the transition of a hypothetical cohort of patients between mutually exclusive health states according to certain transition probabilities over a series of discrete time periods (cycles); each patient is assumed to reside in only one health state at any point in time. These health states represent the most common

events that occur during the disease course: they can be transient states (patients can transit from these states and revert at any time), temporary states (patients can stay in these states for only one cycle) and absorbing states (patients can never exit from these states) (272). Outcome and cost values are assigned to each health state. These values are weighted by the transition probabilities, then the weighted values are summed across the health states for each cycle, and then are summed across all cycles to calculate the expected costs and outcomes (160,272).

One of the key limitations in Markov models is the memoryless feature of the health states, which indicates that the transition probabilities of patients depend only on the current health state and not on the previous health state (211,273,274). This limitation can be overcome by using time dependency in the transition probabilities (173,211). There are two types of time dependency. One is where transition probabilities vary according to the time the cohort spends in the model, i.e. the probabilities change as the cohort is aging (173,211). The other is where the probabilities vary according to the time the cohort spends in a specific health state (173,211). For example, the probabilities of transition from progression-free to local recurrence will depend on how long the patients stayed in the progression-free state.

Patient-level simulations such as the DES allow patients to move individually through the model, and thus, the patients' transition probabilities, expected cost, and outcomes will depend on their past history, and thus, there is no need to include more health states (173). As patients are modelled individually, this will allow consideration of the variability in the events between patients, and thus, will allow more appropriate estimates for the expected cost and outcomes (173).

In the DES, patients move through the model according to the time of the next event, rather than moving in a fixed time interval (i.e. cycle) (275). The DES is a good choice

when patients compete for the same constrained resources, since the patients should wait in a queue until the resources are available to provide service for them (262). DES also can be used when many patients' characteristics must be taken into account, particularly if they change over time (262). However, one of the main challenges of conducting a patient-level simulation model is that it is more demanding for data, and thus, it was not used as frequently as the Markov model in the literature.

In this study, the Markov model was used to compare the lifetime cost-effectiveness of different initial treatments. The previous systematic review results (Chapter 3.) suggested that health states related to breast cancer progression should be included in the decision analytical model for modelling treatment benefit of surgical procedures. However, there was a lack of literature of economic modelling to inform which health states should be included to assess the treatment benefits of PETx. Alternatively, outcome measures used to assess treatment response in patients following their receiving PETx in RCTs and observational studies conducted in older women with primary breast cancer were used to inform the design of health states for the PETx pathways (51).

CUA is the recommended type of CEA by NICE, that uses QALY as the main outcome measure. QALY is not a disease-specific measure, and hence it enables a standardised approach for comparing economic evaluations across different health care areas (276). QALYs consider the impact of the quality of life (QoL) on the length of life and are calculated by multiplying the utility by the LYG. Given that breast cancer and its associated treatments may influence patients' QoL in a long-term, it is important to evaluate their QoL alongside the LYG.

Uncertainty is inherent within all economic evaluations (211), and it may arise from variation around the key parameters estimated (such as transition probabilities,

utilities, costs, and treatment effects), the methods used to evaluate and measure costs and health outcomes (such as discount rate), related to the model structure assumptions, or variability between patients due to their characteristics (i.e. heterogeneity) (160,271,277). To quantify the uncertainty, sensitivity analysis is used to examine the influence of varying parameter estimates across a range on the cost-effectiveness results (278). One of the sensitivity analysis approaches is PSA. PSA involves sampling values from a distribution assigned to the model parameters repeatedly to examine the effect of varying variables simultaneously across a plausible range according to predefined distributions on the cost-effectiveness results (278). This distribution represents the uncertainty around the mean estimate. Gamma and lognormal distribution are the most frequent distributions used to reflect the uncertainty around the highly skewed data such as costs, while beta distribution is most frequently used to reflect the uncertainty around the utility and transition probabilities (211). Thereafter, a random value is selected from the distribution for each parameter using Monto Carlo simulation (211).

PSA has the advantages of exploring the joint uncertainty across all the parameters at the same time (173). In addition, PSA is likely to produce a more robust and realistic estimate of uncertainty since it is based on a large number of simulations (278). In addition, since multiple data sources were used to derive the cost-effectiveness results from an economic model, there is a great deal of uncertainty, which is needed to be quantified and explained. Therefore, the PSA was used to assess the joint uncertainty emerges from all the parameters that were used to generate the cost-effectiveness results at the same time by drawing a random number repeatedly from the assigned distribution for each parameter simultaneously (278).

## 4.2. Aim and objectives

This chapter aimed to estimate the lifetime costs and benefit associated with using PETx against surgery in older women with primary breast cancer using a Markov model technique. The objectives include:

1. To design a Markov model for assessing the cost-effectiveness of PETx and surgery in older women with primary breast cancer
    a. To identify the health states that describe the natural characteristics of disease progression
    b. To derive transition probabilities, the resource use and costs, and utility associated with each health state in the model from multiple sources
2. To conduct a CEA using a Markov model
3. To assess the uncertainty around the cost-effectiveness results
    a. To assess the joint uncertainty around the key parameters using probabilistic sensitivity analysis
    b. To identify the key parameters that have an influence on the ICER results using one-way and scenario sensitivity analyses

## 4.3. Methods

### 4.3.1. Study design

This CUA used a Markov model with a lifetime horizon to compare the lifetime costs and QALYs between the using of PETx against surgery as the initial treatment strategies in a hypothetical cohort of older women with primary breast cancer from the perspective of the UK NHS.

PETx and surgery are the most commonly used initial treatment strategies for older women with primary breast cancer in clinical practice in the UK, despite there is limited evidence to support their long-term effectiveness in this population. This CUA study hypothesised that different treatment strategies will lead to different outcomes and resource use, and instead of focusing on a specific type of PETx or surgical treatment, the cost-effectiveness of treatment strategies comparing PETx against surgery in the UK was evaluated from the UK NHS perspective. QALY was used as the outcome of this economic evaluation to reflect the impact of treatments on QoL as suggested by the NICE guideline (268). A Markov model was used in this study due to its flexibility in modelling multiple recurrence events occurring during disease progression, whilst retaining less complexity in the process of building and analysing the model as compared with other patient simulation models.

A lifetime horizon was chosen to compare differences in long-term outcomes (as survival and QALY) between PETx and surgery (266). The cost and utility were calculated in a one-year cycle length during the lifetime of the hypothetical cohorts. One-year cycle length was chosen, since it was unlikely for two clinical events to occur within one year following the initial treatments according to the previous cohort study (Chapter 2.). The rationale of choosing the one-year cycle length was consistent with the ISPOR recommendation which suggested that the cycle length in Markov models

should be short enough so that multiple changes in disease events or costs are unlikely to occur during one cycle (266).

### 4.3.2. Model design

#### 4.3.2.1. Model framework

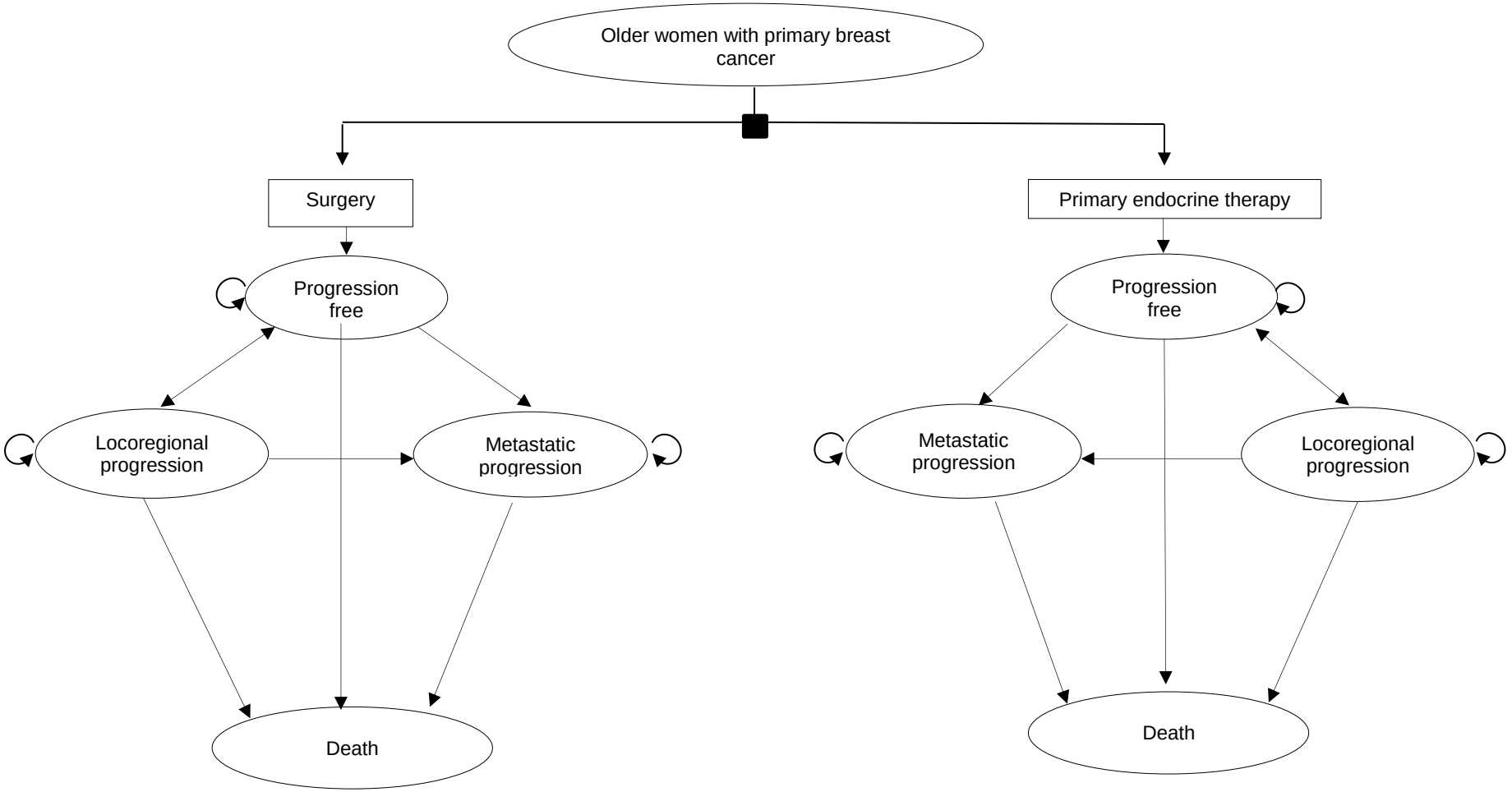
The design of Markov model used in this study was informed by the literature, the results of a systematic review summarising the previous economic evaluations (Chapter 3.), and expert opinion.

The Markov model was conducted on two hypothetical cohorts, including the base case and a subgroup with high ER-positivity (H-score >250). The base case was a hypothetical cohort of older women with primary breast cancer over 70 years who were typical patients recruited in the previous cohort study (Chapter 2.) and published RCTs (5). Subgroup analyses were conducted for older women with H-score >250 since previous literature showed that there is a potential advantage of using PETx in patients with H-score >250 (69).

The Markov model starts from a hypothetical cohort of older women who are diagnosed with primary breast cancer and receive PETx or surgery, breast cancer progression of patients over time varied according to the different initial treatment strategies that patients receive (Figure 4.1.). Patients who receive surgery were assumed to enter the 'progression-free' state of the model where they may (1) remain until they progress to (2) locoregional progression, (3) metastatic progression, or (4) death due to any cause. Patients, who transit from progression-free to locoregional progression health state may either (1) remain there, (2) experience a metastasis, or (3) die. Patients who transit from progression-free to metastasis may (1) remain in this state or (2) die (Figure 4.1.).

Similarly, patients who receive PETx were assumed to enter the ‘progression-free’ state of the model where they may 1) remain or progress to 2) locoregional progression, 3) metastasis, or 4) death due to any cause. Patients, who transit from progression-free to locoregional progression health state may either 1) remain there or 2) experience metastasis or 3) die. Patients who transit from progression free to metastasis remain there until they die (Figure 4.1.).

**Figure 4.1. Markov model structure for a cost-effective analysis comparing surgery against primary endocrine therapy in older women with primary breast cancer**



To reflect the natural disease-progression of breast cancer and the standard treatment pathway of older women with primary breast cancer after having been diagnosed with breast cancer, the Markov model consisted of four main health state, including progression-free, locoregional progression, metastasis, and death (Figure 4.1.). For the PETx group, the different health states used in this economic model were defined according to the 'International Union against Cancer Criteria (UICC) for evaluation of the therapeutic response of systematic therapy in cancer' (279,280) (Table 4.1.). According to the UICC criteria, therapeutic responses to systematic therapy for cancer are categorised into two categories, namely, progression-free and progressive disease (PD) (279). Progression-free disease includes complete response (CR), partial response (PR), and stable disease (SD), whilst progressive disease includes locoregional and metastatic progression (Table 4.2.).

**Table 4.1. The terminologies and definition of the health states included in the model to reflect the natural progression of primary breast cancer in older women**

| Transition state | Definition |
|---|---|
| **Surgery** | |
| Progression-free | Patients enter a period of remission after successful surgical removal of breast cancer and they remain in this state until they die without evidence of disease or are diagnosed with a locoregional or distant relapse. |
| Locoregional progression | Patients have a reappearance of breast cancer in the same breast or in the regional lymph node in the armpit area after the successful removal of breast cancer by surgery. |
| Metastatic progression | Patients have a reappearance of cancer in a distant organ such as bone and liver after the successful removal of breast cancer by surgery. |
| **Primary endocrine therapy** | |
| Progression-free | The tumour remains stable in size or shrinks by 25% from the start of the systemic treatment. The patient remains in this state until the tumour lesion increases in size by 50% or a new lesion appears in the regional lymph node in the armpit area. |
| Locoregional progression | Patients have an increase in tumour lesion size by 50% or a new lesion appears in the regional lymph node in the armpit area after the start of the systemic treatment. |
| Metastatic progression | Patients have a reappearance of cancer in distant organs such as bone and liver after the start of systemic treatment for breast cancer. |

**Table 4.2. Response to systemic therapy for managing breast cancer according to the International Union against Cancer Criteria**

| Category | Definition |
|---|---|
| Complete response | Complete disappearance of the tumour lesion |
| Partial response | More than 50% reduction of the lesion |
| Stable disease | less than 25% increase or less than 50% reduction of the tumour lesion |
| Progressive disease | More than 25% increase of tumour or appearance of new tumour lesion |

#### 4.3.2.2. Model assumptions

Several assumptions were made related to the health states associated with the PETx and surgical strategies (Table 4.3.). The treatment goals for breast cancer management are different between surgery and PETx. The main aim of surgery is to cure breast cancer (44), whilst PETx aims to control the disease progression (44), and therefore, both surgery and non-surgical strategies would have different clinical

outcomes and different transition states. Health states related to the surgical treatment for women with primary breast cancer, which have been summarised in the systematic review, were directly used in this study, including progression-free, locoregional progression, metastasis, and death (Chapter 3). However, since health states related to PETx as an initial treatment were not available from the systematic review, several assumptions were made based on clinical knowledge of the progression of primary breast cancer following PETx, in order to decide the health states in the Markov model for the PETx group (Table 4.3.).

**Table 4.3. Assumptions to supporting the model framework**

| Model assumptions | References |
|---|---|
| • The age of the cohort at the entry into the model was 70 years | Database (Chapter 3) and SR of RCTs (51) |
| • Types of models and key transition states used for patients younger than 65 years old in the literature are applicable to older women over 65 years | SR of EE (Chapter 5) |
| • Types of models and transition states used for modelling surgery as the initial treatment in the literature can be directly used to model the surgical pathway for treating older women with primary breast cancer | SR of EE (Chapter 5) |
| • Local recurrence, regional recurrence, and contralateral tumour can be combined as a single health state | SR of EE (Chapter 5) |
| • Metastasis should be a stand-alone health state | SR of EE (Chapter 5) |
| • Clinical outcomes used to measure response to PETx in the literature can be used to model the PETx health states | SR of RCTs and observational studies(51) |

**(Note)** SR: systematic review; EE: economic evaluation; RCTs: randomised controlled trials.

Clinical outcomes associated with a response to PETx as an initial treatment were reported in several RCTs and observational studies in older women with primary breast cancer (Chapter 1.). These studies used the *UICC criteria for evaluation the therapeutic response of systematic therapy in cancer* to assess the efficacy of PETx in women with primary breast cancer (46,71,73,75,76). Therefore, it was assumed that these clinical outcomes used to measure response to PETx in the literature can also be used to model the PETx health states for treating older women with primary breast cancer in the long term.

Several retrospective analyses of patients with metastatic or primary breast cancer who received ETx as a primary treatment have shown that the survival rates for patients who achieved SD at 6 months were the same as those for patients who achieved CR or PR at 6 months (199,281). Therefore, an assumption was made that these three subcategories (i.e. CR, PR, and SD) can be combined in one health state because they present a similar treatment outcome and disease progression for breast cancer. Similar to the assumption for surgical pathways, local and regional progressions were assumed to be combined in one health state. However, metastatic progression was assumed to stand alone as a separate health state (Chapter 3.).

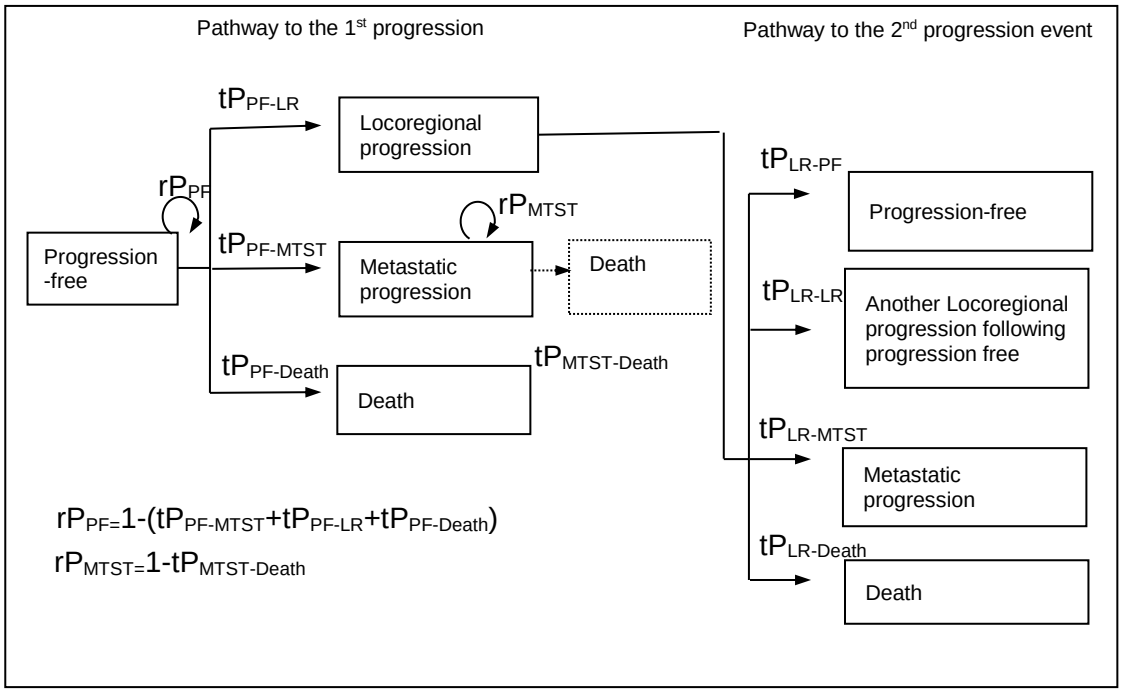
### 4.3.3. Data sources

Multiple data sources were used in this study to derive the key parameters required for conducting the Markov modelling, such as transition probabilities, health care resource use and cost, and utility for each health state.

#### 4.3.3.1. Transition probabilities

Transition probabilities from the progression-free to the first progression events (i.e. locoregional or metastatic progression, or death), and from the first to the second progression events were derived for each treatment group separately from the previous cohort study (Chapter 2.) using a local hospital's registry of older women with primary breast cancer (Chapter 2.) (Figure 4.2.).

**Figure 4.2. Initial and subsequent transitions estimated using parametric regression**




Note: $tP_{PF\text{-}MTST}$ is the transition probability from progression-free to metastasis; $tP_{PF\text{-}LR}$ is the transition probability from progression-free to local recurrence; $tP_{PF\text{-}Death}$ is the transition probability from progression free to death; $rP_{MTST:}$ is the probability of remaining in the metastatic state; $rP_{PF:}$ is the probability of remaining in the progression-free state; $tP_{LR\text{-}LR:}$ is the transition probability from local recurrence to local recurrence; $tP_{LR\text{-}PF:}$ is the transition probability from local recurrence to progression free; $tP_{LR\text{-}MTST:}$ is the transition probability from local recurrence to metastasis; $tP_{LR\text{-}Death:}$ is the transition probability from local recurrence to death.

In the cohort study, patients who were treated by either surgery or PETx as the initial treatment strategy were followed after receiving the treatment to the final record in the registry or death, and progression events and time to progression events were measured for both groups, respectively (Figure 4.2.).

To calculate the transition probabilities from progression-free to subsequent events, the first progression events that patients experience (i.e. locoregional progression, metastatic progression, or death), and time to that event (i.e. time since patients' treatment until experiencing the event) were identified. Likewise, to calculate the transition probabilities from the first to the second progression events, the second progression events that patients experienced (i.e. another locoregional progression, metastasis, death following locoregional progression, or death following metastasis) and time to second events were also identified (i.e. the time since patients' treatments until the occurrence of the second event.

With each cycle elapsed, the cohort will get older and they are at risk of death from causes other than breast cancer, i.e. age-dependent mortality. Previous literature demonstrated there was a comparable incidence of comorbidities between breast cancer survivors aged over 65 years old and their matched women of same age without breast cancer (282,283); therefore, an assumption has been made that non-breast cancer mortality rates in patients with breast cancer who are in disease-free state are similar to the non-breast cancer mortality rates of the general population, and thus two approaches were used to estimate the transition probabilities, including Weibull model and another from the national life table. The age-specific non-breast cancer mortality rates in 2014 were calculated by subtracting breast cancer mortality from all-cause mortality derived from the UK national life table from the office for national statistics (ONS) (284)(Table 4.4.). Since mortality rates were presented per

1,000,000 population per year, annual transition probabilities per patient in the model were calculated by dividing the mortality rate by 1,000,000.

**Table 4.4. Age dependent transition probabilities based on the national life table (284)**

| Age (years) | All-cause mortality | Breast cancer mortality | Non-breast cancer mortality |
|---|---|---|---|
| **Proportions (per 1,000,000 population per year) by age** | | | |
| 65-74 | 12003 | 731 | 11272 |
| 75-84 | 37731 | 1294 | 36437 |
| 85-90 | 95434 | 2251 | 93183 |
| 90 over | 198983 | 3492 | 195491 |
| **Yearly transition probabilities by age** | | | |
| 65-74 | 0.012003 | 0.000731 | 0.011272 |
| 75-84 | 0.037731 | 0.001294 | 0.036437 |
| 85-90 | 0.095434 | 0.002251 | 0.093183 |
| 90 over | 0.198983 | 0.003492 | 0.195491 |

#### 4.3.3.2. Health care resource use and costs

Health care resource use related to different health states in the model was also estimated based on the previous cohort study (Chapter 2.). Since the majority of resource use related to the disease diagnosis and progression, including treatment related to recurrence, are incurred in the secondary care, only the resource utilisation related to the secondary care was included in this analysis. Health care resource utilisation in secondary care, including different types of treatment, outpatient visits, and MDT meetings was identified from the corresponding variables recorded in the cohort database (Chapter 2.) and was further grouped according to patients' health states and initial treatment strategies, i.e. surgery or PETx.

Patients in the progression-free state incurred the resource use of initial treatment, adjuvant therapy (in the case of surgery), and follow-up (Table 4.12.). The resource use for patients who remained progression-free in the subsequent cycles were calculated according to the initial treatment that patients received. The resource use incurred by patients who received PETx as the initial treatment in the subsequent cycles were assumed as similar to those of the first cycle (Table 4.13.). Given that the resource use utilisation of surgery and adjuvant ETx incurred by patients who received surgery as the initial treatment only for one and five years, respectively, and thus, the frequency of follow-up and adjuvant therapy only incurred in the second to the fifth cycles following the initial treatment, whilst only the frequency of follow-up incurred after 5 years (Table 4.14.).

The resource use of treatment for locoregional recurrence, including surgical or non-surgical treatments, new admission, MDT meeting, CT scan, and follow-up incurred by patients in the locoregional state (Table 4.15.). The resource use of non-surgical treatments and follow-up incurred by patients who remained in the locoregional state for the next cycle (Table 4.16.). The resource use of non-surgical treatment, new

admission, follow-up costs, MDT meeting, and CT scan incurred by patients in the metastatic state (Table 4.17.), whilst the resource use of treatment and follow-up incurred by patients who remained in the same metastatic state for the next cycle (Table 4.18.).

#### 4.3.3.3. Utilities

***Data source***

Utilities attached to each health state, namely progression-free, locoregional recurrence, metastasis, and death states, for each treatment strategy were derived from multiple data sources (Table 4.5.). Zero utility value was attached to the death state. Ideally, utility values should be measured at a different time for different health states in older women with primary breast cancer in the simulated cohort study. However, there is limited information from currently available literature to derive utilities for different states at different time points.

Utility values were derived from literature, including Prescott *et al.* (2007) (1), Fallowfield *et al*. (1994) (285), and Peasgood *et al*. (2010)(2). Prescott *et al.* (2007) reported the utility values related to progression-free state within one year for patients who received surgery, which was identified from a systematic review conducted by Peasgood *et al*. (2010) (2).

Peasgood *et al*. (2010) systematic review conducted by health economists at the University of Sheffield that searched 13 databases until March 2009 to summarise all the health state utility values for early and metastatic breast cancers and to identify the factors influencing the utility value estimates. Of the 49 articles included in the systematic review, 29 studies reported health state utility values for primary breast cancer, while 20 reported health states related to metastasis (2).

Only one study of the 49 studies evaluated health states related to older patients with primary breast cancer, which is Prescott *et al*. (2007) (1). Prescott *et al*. (2007) study evaluated the utilities related to 255 patients over 65 years old from cancer clinics in the UK, who were at low risk of recurrence and axillary node-negative breast cancer (T0–2, N0–1, M0) and were randomised to receive BCTx plus ETx or BCTx plus ETx

plus RTx, at baseline, 3.5, 9, and 15 months using the EQ-5D UK tariff (1). This study showed that the mean utility values were 0.77, 0.78, 0.76, and 0.74 for patients who received breast conservation therapy plus ETx plus RTx at baseline, 3.5, 9, and 15 months, respectively, while mean utility values were 0.74, 0.76, 0.72, and 0.73 for patients who received breast conservation therapy plus ETx at baseline, 3.5, 9, and 15 months, respectively (1). However, this one study evaluated the utilities for patients who received surgery as the main treatment; patients in this study did not receive PETx as the main treatment. The utility measured in older women with primary breast cancer received PETx is expected to be different from the utility measured in those who received surgery as an initial treatment. Since PETx aims to slow tumour progression rather than cure it, the additional concern of cancer recurrence due to the persistent presence of the palpable lump would negatively affect their QoL (219). Moreover, the profiles of adverse events between PETx and surgery are different, and thus may incur a different impact on QoL.

Therefore, in collaboration with an undergraduate research project in the School of Pharmacy at University of Nottingham, an update for this systematic review was conducted to identify any study reported utility value for older women, particularly who received PETx and published between March 2009 until March 2015, using the same search strategies developed in the previous systematic review (286). Of the 15 included articles (287-301) included in this updated review, 11 papers were related to an early breast cancer (288,290-292,295-301) and four related to metastasis (289,292,297,302). However, none of these studies reported utilities related to older women over 70 years. Therefore, the only available data to derive utility value in the first year following surgery was from Prescott *et al.* (2007) since it closely matches the recent subset of the cohort in terms of age (over 70 years) and tumour stage (T0–2, N0–1, M0) (Section 1.2.3.1) (1).

Thus, for the utility values of PETx, and the long-term change in utility values with time due to the treatment (either surgical of PETx) were derived from Fallowfield *et al*. (1996) study that compared the Qol of 98 older women over 70 years old with primary breast cancer and fit for surgery, who were randomised to receive the treatment with either surgery plus tamoxifen or tamoxifen (defined as T1, T2, T3a, N0 or N1, and M0), at three months and two years posttreatment using general health questionnaire (GHQ)-28. Both treatment groups were well matched with regard to prognostic factors (i.e. tumour stage, nodal status, and tumour size) and age (285).

Results from the GHQ-28 at 3 months showed a small statistically significant advantage to the tamoxifen alone group by 0.14 as compared to surgery, but at 2 years, there was no statistically difference in QoL between both groups with an improvement in QoL by 0.06 following surgical group whereas that PETx's Qol was getting worse two years following the PETx by 0.08. However, the actual QoL data was not available from this questionnaire, and it is could not be mapped to the EQ-5D since GHQ-28 is not available to be mapped to EQ-5D (285). In addition, GHQ is out of the dated questionnaire that is not commonly recommended to be used by NICE as a mapping method (i.e. using statistical model that can be used to predict the utility values of EQ-5D using the QoL data available from non-preference based measures such as the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire) (303).

Therefore, for deriving the utility value of PETx, the indication from Fallowfield that the QoL of patients who received PETx was higher by 0.14 as compared to surgery was added to the first-year utility following surgery, which was derived from Prescott. *et al.* (2007) (1). For the improvement of utility with time in case of surgery, the 0.06 improvement in QoL, reported in the Fallowfield *et al.* (1996) was added to the first-year utility following surgery whereas for the decrement of utility with time in case of

PETx, the 0.08 decrement in QoL, reported in the Fallowfield *et al.* (1996) was added to the first-year utility following PETx (285).

Utility values related to the local and metastatic recurrence were derived from the meta-regression model by Peasgood *et al*. (2010) systematic review. This meta-regression was conducted to predict the utility values for younger patients with primary and metastatic breast cancer, respectively based on independent variables (2). The independent variables' coefficients represent the value by which the primary or metastatic breast cancer utility value is improved or worsened; positive values indicate an improvement in utility values, whereas negative values indicate a worsening in utility values. The independent variables for primary breast cancer, including treatment regimens, choice of valuation method, local recurrence, the time when utilities are valued, and the respondents who valued the health states had significant impacts on utility values in patients with primary breast cancer (2), whilst for patients with metastasis, the independent variables, including the types of treatment, choice of valuation method, response to treatments, respondents who valued the health states, and side effects had significant impacts on their utility values (2) (Table 4.7.). The marginal disutility decrement as a result of local recurrence was added to the utility values following the initial diagnosis whereas the metastatic utility was predicted based on the types of treatment, choice of valuation method, response to treatments, respondents who valued the health states, and side effects.

For long-term change with time as the cohort is aging. The marginal coefficient of age for each year, derived from the shelf-off method catalogue of the UK (-0.0003* number of years passed) were added for all health states to reflect the impact of age itself. An ''off-the-shelf'' catalogue of EQ-5D scores provides a standardised source of the general population utility scores for a variety of condition after controlling for comorbidities, age, gender, race, income, and education that can be used in QALY

estimation. This age coefficients represent the marginal decrement in EQ-5D index scores for each condition after controlling for age, comorbidity, gender, race, ethnicity, income, and education (304).

**Table 4.5. Utility values available from literature**

| Utility components | Values (95%CI) |
|---|---|
| **Primary breast cancer** | |
| Progression-free state within one year | |
| Surgery | 0.76 (0.73, 0.79) |
| Utility improvement for PETx as compared to surgery | 0.14 (NA, NA) |
| Progression-free state over one year | |
| Utility improvement for surgery | 0.06 (NA, NA) |
| Utility decrement for PETx | 0.08 (NA, NA) |
| Local recurrence | |
| Utility decrement as a result of local recurrence | 0.01 (NA, NA) |
| **Metastatic breast cancer coefficients for the independent variables used to generate the metastatic utility values** | |
| ***Type of treatment*** | |
| Tx-nonspecific | 0.02 (-0.04, 0.07) |
| ***Type of response to treatment*** | |
| Response non specific | -0.27 (-0.32, -0.21) |
| ***Who valued the utility*** | |
| Patients' scenario | 0.17 (0.06, 0.19) |
| ***Valuation methods*** | |
| EQ-5D UK | 0.02 (-0.05, 0.08) |
| Constant | 0.64 (0.59, 0.69) |

**(Note)** EQ-5D: European Quality of Life-5 Dimensions; UK: United Kingdom; PETx: primary endocrine therapy

### *Assumptions related to utility values*

There is a lack of annual utility changes for health states, including locoregional progression (LP) for surgery and PETx, long-term (i.e. more than one year) utilities, including progression-free (PF), LP, and metastasis for the surgery and PETx. Therefore, several assumptions were made to calculate the one-year and long-term

utilities for different health states related to surgery (PF, LP, and metastasis) and PETx (PF, LP, and metastasis) (Table 4.6.).

**Table 4.6. Assumptions related to utility values**

| Model assumptions | References |
|---|---|
| • Utility values were improved by 0.06 and gotten worse by 0.08, two years following receiving the initial treatment of surgery and PETx, respectively, and thereafter remained constant | (285) |
| • Similar utility values for breast cancer survivor after one year following the initial treatment | (305,306) |
| • Patients have similar utilities of metastatic state regardless their initial treatments, since patients would receive similar treatment for metastasis regardless their treatments | |

The utility values of the progression-free and local progression states over two-years following receiving treatments were assumed to be higher than those utilities measured at less than one year (Table 4.6.). In addition, long-term utility values of those health states were assumed to remain the same after two-years of receiving the treatments in breast cancer survivors. Previous literature demonstrated a significant improvement in the utilities during the first year after receiving treatment, whilst a slight improvement in QoL and utility was evident in patients who remained DF over one year (305,306). Hsu *et al*. (2013) conducted a prospective cohort study of 535 women with primary breast cancer (mean age of 49.8, SD: 8.9) years to estimate the QoL of breast cancer survivors at the disease-free state after initial treatment. The results showed a significant improvement in several QoL domains within the first year after breast cancer diagnosis and operative treatment, but there was only a slightly improvement over subsequent years during long-term follow-up (mean: 12.7 years, range: 9.4 to 17.6 years). In addition, the QoL of breast cancer survivors after the long-term follow-up was similar to the age-matched general population who are free of breast cancer (305).

Moreover, Ko *et al*. (2003) conducted a prospective study which assessed the utility of breast cancer survivors of newly-diagnosed breast cancer (mean age of 56, SD: 15 years) following surgical treatment and receiving adjuvant tamoxifen, and the results showed that health utility scores were the lowest immediately after surgical treatment (0.62) and improved over time. There was a modest difference in utilities between survivors at 1-5 years (0.67) and long-term (>5 years) (0.69) (306).

Utility related to metastasis was assumed to remain constant with time due to the lack of long-term utility data following metastasis (2).

**Table 4.7. Utility values of different health states**

| Health states by the initial treatment | Utility values | References |
|---|---|---|
| **Surgery** | | |
| Progression-free state | | |
| *1 year* | 0.76 | Prescott. *et.al* (2010) (1) |
| *> 1 year* | 0.82 | Prescott. *et.al* (2010) (1), Fallowfield. *et.al* (1996) (285) |
| Locoregional progression state | | |
| *1 year* | 0.75 | Meta-regression of a systematic review (2), Prescott. *et.al* (2010) (1) |
| *> 1 year* | 0.81 | Meta-regression of a systematic review (2), Prescott. *et.al* (2010) (1) |
| Metastasis | 0.53 | Meta-regression of a systematic review (2) |
| **Primary endocrine therapy** | | |
| Progression-free state | | |
| *1 year* | 0.90 | Prescott. *et.al* (2010) (1), Fallowfield. *et.al* (1996) (285) |
| *> 1 year* | 0.82 | Prescott. *et.al* (2010) (1), Fallowfield. *et.al* (1996) (285) |
| Locoregional progression state | | |
| *1 year* | 0.89 | Meta-regression of a systematic review (2), Prescott. *et.al* (2010) (1) |
| *> 1 year* | 0.81 | Meta-regression of a systematic review (2), Prescott. *et.al* (2010) (1) |
| Metastasis | 0.53 | Meta-regression of a systematic review (2) |

### 4.3.4. Data analysis

#### 4.3.4.1. Transition probabilities

Time to progression events and number of progression events identified from the previous cohort study (Chapter 2) were used to estimate the annual hazard rate (i.e. risk of events) for each progression event using a parametric model. Hazard rates were later used to predict the annual transition probabilities for each transition state in survival analyses, which incorporate censored data in the analysis. The COX model did not assume the hazard rate to follow a particular distribution; it only estimates the hazard rate based on the observed data available within the longitudinal database follow-up. However, parametric models assume the hazard rates to follow a particular distribution and thus, have advantages over COX regression since they predict and extrapolate the risk of events beyond the available data within the observational study follow-up period to a long-term time horizon, and thus, were used to inform the change of transition probabilities with time, i.e. time-dependency in the Markov model (307).

However, similar to the COX regression, the parametric regression model assumes a proportional hazard ratio between both treatment groups, and thus, parametric models to each treatment arm were fitted separately to allow for time-varying hazard ratios (307). Different parametric models, including Weibull, Gompertz, and log-logistic models were tested to check which of these distributions fits (i.e. the differences between the observed hazard rates during the follow-up period and the ones predicted using the assigned distribution are not statistically significant) the observed hazard rates during the longitudinal database follow-up using a Wald test. The Wald test was used to test the shape parameters of these models with a P-value >0.05 indicated that there was no significant difference between the observed and predicted distribution) and this indicates that the chosen model was the most appropriate model to fit the survival data.

In this study, the hazard rates (of annual progression events) were predicted by age and ER status rich positive, clinical size in a parametric regression model for each event in patients who received PETx or surgery, respectively. These covariates have been shown to influence the transition to recurrence, death, or both; advanced age is associated with increase risk of death from causes other than breast cancer, and thus, would influence the transition to overall death (69). ER status, clinical size, axillary stage impact the risk of recurrence and breast cancer death, and thus would impact the transition to recurrence and death (6). However, given that axillary stage was only recorded for the surgical treatment, ER status, and age were included as the predictors in the parametric regression.

Age was considered as a continuous variable, whereas ER status was considered as a categorical variable, including ER negative, positive (H-score <=250), unknown, and rich positive (H-score >250) status. Hazard rates for the first event (the risk of the first progression events) were regressed only against age and ER status. Given that the hazard rates of second event depend also on the types of first events, the hazard rates of second events were regressed against types of the first events in addition to age, and ER status.

The Weibull model was identified as the best-fit model to estimate the hazard rate. Two parameters, namely gamma and lambda, which represent the hazard function distribution, were estimated. The gamma parameter, γ, is the 'shape parameter' that represents how the hazard rates change with time: thus γ<1 indicated that the hazard rate decreased with time, γ>1 indicated that the hazard rate increased with time, γ=1 indicated that the hazard rate remained constant with time (308).

Lambda parameter, λ, is the 'scale parameter' that represents the dispersion of the distribution. If it is large, then the distribution will be more spread out; if it is small then it will be more concentrated (308).

The gamma parameter was identified directly from the STATA output for the Weibull regression using the streg command, whilst the lambda was calculated from the parametric regression model. Since the estimation of the parametric regression model was undertaken on the log-hazard scale, i.e. the relation between the hazard rate and the independent variable coefficients were linear in the log scale, thus, exponentiating all the independent variable coefficients gave the relative hazard rate (i.e. hazard ratio) of each covariate compared with their reference group, i.e. the percentage of increasing or decreasing in the hazard rate which is contributed to each covariate compared to their baseline group (173,308).

Lambda defined the baseline hazard for the starting cohort, and thus it was calculated using the Weibull model calculation on the log scale (173):

Log H(t) = Constant + ERstatusC*ERstatus value + AgeC*Age value

Log Lambda was calculated as the linear sum of the coefficients multiplied by the dependent variables using the following equation (173):

Log λ = Constant + ERstatusC*ERstatus value + AgeC*Age value

where 'constant' represents the baseline hazard ratio when other covariates set the reference group, i.e. age is zero and ER status is ER-negative status; ER statusC is the ER status coefficient, which represents the relative change in hazard rate for each ER status category, including positive, unknown, and richly positive compared with the reference group (which is ER-negative status); AgeC is the age coefficient, which represents the relative change in hazard rate with each change in one year.

Starting age of 70 years and ER-overall status (i.e. without specifying the ER status), whereas starting age of 70 years and ER-positive status over 250 were used to estimate λ to predict the transition probabilities to first and second events for the base case and subgroup analyses, respectively.

The λ and γ parameters that were derived based on the assigned hazard function were later used to estimate the annual transition probabilities based on the following equation (173):

tp (tu)=1-exp (λ(t-u) γ- λt γ)

Transition probabilities derived from this equation tp (tu)=1-exp(H(t-u)-H(t))

Hazard function H(t) for Weibull regression model derived from this equation $H(t)= \lambda t^{\gamma}$

Thus, transition probabilities estimated based on Weibull regression tp (tu)=1-exp (λ(t-u) γ- λt γ)

where tp(tu) is the transition probabilities at time t

λ is the scale parameter

γ is the shape parameter

u is the cycle length

The yearly transition probabilities for the first and second events for each treatment were presented.

#### 4.3.4.2. Costs

Direct medical costs incurred in the secondary care were calculated by multiplying the quantity of each resource use item by its unit cost and reported in UK pounds (£) at 2014 prices. Diagnostic procedures and capital costs were excluded from the health care resource utilisation because they were incurred in advance when the hospital had

been constructed (Chapter 2) (143,160). Unit cost for resource use was estimated based on the BNF and England NHS reference cost (Chapter 2).

The costs of each health care resource use for each health state were grouped based on their resource use categories (i.e. whether an initial treatment, adjuvant treatment, or follow-up cost). Thereafter, within each resource use category, each possible treatment was multiplied by the proportion of patients (i.e. number of patients who received the treatment divided by the number of patients who received the resource use category) who received this treatment in the cohort database. For example, the cost of mastectomy was multiplied by the proportion of patients who received mastectomy (number of patients who received mastectomy divided by the number of patients who received surgery), then the total costs were summed across the different resource use categories. The costs for the subgroup analysis of patients who have an H-score >250, including the costs of each resource use for each health state were generated separately for patients within the subgroup using a similar procedure to that mentioned above.

Zero costs were attached for patients in the death state. An annual discount rate of 3.5% according to the NICE guideline recommendation (268) was applied for all future costs and QALYs using the following equation:

$1/(1+r)^n$ where r refers to the discount rate and n refers to the number of years

Discounting reflects the fact that people prefer to spend money on resources now rather than in the future, i.e. positive time preference, thus, it converts the value of future costs and benefits into their present value to allow the standardisation of different costs and QALYs incurred through different times, hence, total costs and QALYs can be compared (309). Generally, discount rate is applied when the interventions last for more than one year (143).

#### 4.3.4.3. Cost-effectiveness analysis

Relevant costs and associated QALYs were assigned to each health state in the Markov model and weighted by the transition probability (proportion of patients transiting to each health state within an one-year time), and then summed up across all the heath states to derive the aggregated costs and QALYs in a yearly cycle. The mean costs and QALYs were continuously calculated in each yearly cycle until a terminating condition is met (99% of patients died).

Since a Markov model assumes that patients transit to health states at a discrete point in the cycle. However, in reality patients may move into another health state at any point during the cycle. For example, assuming that all patients who die do so at the beginning of a cycle (as opposed to at some point during the cycle) underestimates survival, and thus, QALY accumulation. And therefore, a half cycle correction was applied to all cost and utility values attached to health states by assigning a half-payoff (i.e. adding 0.5 to the total life expectancy, and adding half of the first cycle worth of cost and utility to the total cumulative cost and utility for each treatment in the model) in the first cycle to adjust for the underestimation (211).

#### 4.3.4.4. Probabilistic sensitivity analysis

PSA was used to explore the impact of joint parameter uncertainty on the cost-effectiveness results, which involved measuring the effect of varying estimated values of all parameters simultaneously by making distributional assumptions for transition probabilities, costs, and utilities for the base case and subgroup analyses (173,278).

***Multivariate normal distribution for transition probabilities***

Multivariate normal distribution on the log scale was assumed for the coefficients derived from the Weibull models, including λ, γ parameters, type of events, age and ER status coefficients for each transition probability, since they are normally distributed

on the log scale; multivariate refers to the correlation amongst the coefficients. In order to consider the correlation between the coefficients within the Weibull regression model, a correction factor (T*Z) was added for the actual coefficient on the log scale (y) derived from the Weibull regression. T refers to the correlation factor of each coefficient with the others, which is derived from a Cholesky's decomposition matrix, i.e. the variance-covariance matrix that provides the correlation between the coefficients. Z refers to the random value drawn from the normal distribution. Thus a multivariate, i.e. a correlated random normal variable (x) for each coefficient was generated using the following equation (173):

$X = Y + T*z$

Using the multivariate normal distribution provided correlated draws from this distribution assigned for regression coefficients using Cholesky decomposition rather than attaching independent normal distributions to each parameter coefficient using point estimates and standard errors from the Weibull regression model outputs. Therefore, it allows accurate presentation of uncertainty in the transition probabilities by considering any potential correlation between the regression coefficients identified by the chosen parametric survival model.

***Gamma distribution for unit costs***

All unit costs were assigned a gamma distribution, since this distribution reflects the typically strong positive skewness in cost variables (173). Uncertainties around the unit cost sourcing from the England NHS reference costs, including surgical, RTx, CTx, outpatient visits, and CT scan were presented as lower and upper quartile estimates. These estimates were used to derive the gamma distribution parameters. Unit costs derived from the BNF, including medication costs, were held constant, since they are standardised charges across the health care system (Table 4.8.).

Usually, the gamma distribution is characterised by two moments, α and β, which are described by the mean (μ) and standard error (σ). They are calculated as follows:

$\alpha = \mu 2/\sigma 2$

$\beta = \sigma 2/\mu$

However, given that interquartile estimates were only available to derive the gamma distribution, α and β parameters, which are required for defining the gamma distribution, were derived from the output results using the in 'nls' function R program, which is based on the non-linear least squares method. This non-linear least squares method is a non-linear regression that is used to fit a model for a set of observations that are not linearly related (310,311) (Table 4.8.).

**Table 4.8. The uncertainty around the unit cost parameters (204)**

| Resource | Unit costs (IQR) | Alpha | Beta |
|---|---|---|---|
| **Surgery** | | | |
| WLE | 2635 (2056.3, 3120.16) | 10.87 | 250.00 |
| Mastectomy | 2635 (2056.3, 3120.16) | 10.87 | 250.00 |
| Axillary clearance | 2109.73 (1596.71, 2347.14) | 12.62 | 100.00 |
| **CTx** | | | |
| FEC 75 | 284 (159.19, 298.14) | 4.93 | 50.00 |
| FEC 100 | 284 (159.19, 298.14) | 4.93 | 50.00 |
| CTx delivery cost | 165 (79.6, 188.31) | 2.74 | 50.00 |
| Docetaxel | 576 (391.85, 574.61) | 12.73 | 33.33 |
| **RTx** | | | |
| Delivery of RTx | 126 (100.54, 154.33) | 10.31 | 12.50 |
| Planning of RTx | 796.92 (601.19, 938.41) | 2225.36 | 0.46 |
| **Outpatient** | | | |
| Follow-up | 119 (88.71, 139.64) | 9.15 | 12.50 |
| New admission | 169(125.73, 203.25) | 8.20 | 20.00 |
| MDT | 86(52.91, 102.1) | 4.52 | 16.67 |
| CT scan | 129(94.31, 161.48) | 6.59 | 20.00 |

**(Note)** WLE: Wide local excision; FEC: Fluorouracil (5FU), epirubicin and cyclophosphamide; CTx: chemotherapy; CT: Computerised Tomography; RTx: radiotherapy; MDT: Multidisciplinary Team

### *Beta distribution for utility values*

Utilities are restricted to a range between 0 and 1. The beta distribution was therefore deemed to be an appropriate distribution (Table 4.9.). The Beta distribution is characterised by two moments, α and β, which are described by the mean (μ) and standard error (σ). They are calculated as follows.

$\alpha = \mu^2/ \sigma^2 = \mu*(\mu *(1 – \mu)/ (\mu^2) – 1)$

$\beta = \sigma^2/ \mu$

**Table 4.9. The uncertainty around the utility components**

| Utility components (Reference) | Values (95%CI) | Alpha | Beta |
|---|---|---|---|
| **Progression-free state within one year (312)** | | | |
| Surgery | 0.76 (0.73,0.79) | 615.34 | 194.32 |
| **Metastasis (286)** | | | |
| Tx-nonspecific | 0.02 (-0.04, 0.07) | 0.40 | 22.95 |
| Response non specific | -0.27 (-0.32, -0.21) | 126.02 | -598.02 |
| Patients' scenario | 0.17 (0.06, 0.19) | 12.85 | 89.14 |
| EQ-5D UK | 0.02 (-0.05, 0.08) | 0.27 | 15.33 |
| Constant | 0.64 (0.59, 0.69) | 207.76 | 116.87 |

**(Note)** PETx: primary endocrine therapy; Tx: treatment; EQ-5D: European Quality of Life-5 Dimensions; UK: United Kingdom

***Define output variable***

The net expected cost and outcome of each treatment strategy, and the incremental cost and outcome of PETx against surgery were defined to be the output variables of the simulation result. Monte Carlo simulation for 10,000 iterations was run simultaneously for each treatment group to assess the uncertainty around the parameters using Microsoft Excel 2010. Monte Carlo simulation involves selecting random values from the assigned distribution for each key parameter of the model, then the model runs repeatedly for each combination of parameter estimates and the resulting cost and effect pairs are recorded. Each iteration represented one set of outcomes in terms of incremental costs and outcomes (173). Repeating this simulation in a large number allows producing a distribution of possible cost and outcome results (173).

The estimated discounted mean costs, LYGs, and QALYs of the 10,000 simulations for PETx and surgery groups with 95% confidence interval around the mean, as well as the incremental mean costs, LYGs, and QALYs were presented in both disaggregate and aggregate form for the simulation results of base case and subgroup analyses.

***Cost-effectiveness plane***

Each incremental mean cost and effect pair per patient for each simulation was plotted as a point on the cost effectiveness (CE) plane where the x-axis represents the incremental effectiveness (relative to surgery) while the y-axis represents the incremental costs. Points in the northwestern (NW) quadrant imply that PETx dominates the surgery, i.e. PETx is less costly and more effective. Points in the southeastern (SE) quadrant imply that surgery is cost-effective, i.e. surgery is less costly and more effective, so it dominates PETx. Points in the northeastern (NE) and southwestern (SW) quadrants may imply that surgery is cost-effective based upon whether the ICER or ICUR is below the decision-maker's WTA for one QALY loss. The CE plan and CEA curve were presented for only the base case and the patients with complete records on effectiveness.

***The cost-effectiveness acceptability curve***

The probability that PETx is more cost-effective than surgical group for a range of the decision-maker's WTP(λ) for an extra LYG or QALY were presented on the cost-effectiveness acceptability curve (CEAC). The CEAC was constructed by plotting the proportion of the incremental cost-effect pairs (x-axis) that were cost-effective for a range of λ values (y-axis) (313-315). These proportions were calculated by dividing the number of the incremental cost-effect pairs, lying to the south and east of a ray with a slope equivalent to λ in the cost-effectiveness plan, over the total number of cost-effect pairs (313-315). This process was repeated numerous times with different values of λ ranging from 0 to £30,000, which is the maximum threshold that the decision-maker is willing to pay for each QALY as recommended by NICE (313-315).

Incremental cost-utility ratios (ICURs) were used to compare the cost-effectiveness of each alternative from the simulation results. CEACs were produced to reflect uncertainty in costs and effects at different maximum WTA by decision-makers.

Uncertainty around the mean ICUR was presented in CEAC and CE plans for the base case and subgroup analyses.

#### 4.3.4.5. Sensitivity analysis

Series of one-way and scenario sensitivity analyses were undertaken to assess the robustness of findings of base case analysis by changing model input variables and assumptions. Scenario analysis was used to assess the impact of varying assumptions of the transition from either progression-free to overall death or metastasis to overall death on the cost-effectiveness results. One-way analysis, which involves varying one parameter individually, was conducted by varying the values of utilities, and costs to the highest and lowest possible values of their 95% confidence intervals, or interquartile range, to examine the impact of these variations from the mean values on the cost-effectiveness results. Both types of sensitivity analyses allow identifying key model parameters that may influence or change the treatment selection.

The effect of changes in key parameter values or assumptions on treatment selection was measured by net monetary benefit (NMB), which was calculated by the following equation based on the deterministic results using Microsoft Excel 2007:

$NMB = (QALY_{PET} - QALY_{surgery})*WTA - (Cost_{PET} - Cost_{surgery})$

NMB is the difference between the monetary value of the decremental health benefit and decremental cost of PETx as compared to surgery. Positive NMB indicates that PETx is cost effective, whilst negative NMB indicates the PETx is not cost-effective compared with surgery. Using NMB has advantages over ICER in the one-way and scenario sensitivity analyses since it explicitly incorporates the decision-maker's WTA and it is easy to interpret the change in the NMB compared with ICER results. A WTA of £20,000 per QALY, as recommended by NICE was used to generate the NMB.

The WTA threshold reflects the opportunity costs, in terms of scarifying in one QALY's worth of health, resulting from displacing other programmes by new and more costly programmes (268,316). A range of WTA threshold values from £20,000 to £30,000 per QALY was considered by the NICE Technology Appraisal Committee; new or existing treatment with ICER less than £20,000 was accepted by NICE (268). For treatments with ICER higher than 30,000, accepting the treatment will be based on several factors, including the level of uncertainty around the ICER estimates and the social value judgment (317).

The NMB results of the scenario and one-way sensitivity analyses were presented in a tornado diagram. The tornado diagram is a type of bar chart where the x-axis represents the results of economic evaluation, i.e. the NMBs resulted from changing the key parameters and assumptions in the one-way and scenario sensitivity analyses, respectively, whilst the y-axis represents the key parameters that were changed to their specific range. Model parameters, that were tested in the sensitivity analysis, were grouped into three categories, including transition probabilities, costs, and utilities. Tornado diagrams, using Microsoft Excel 2010, were presented for each group of parameters to assess the extent to which variation in expected values of these parameters may change the selection of the alternative strategies.

***Transition probabilities***

The Age-dependent transition probabilities were plotted with the ones derived from the cohort database using Weibull regression to check if there were any discrepancy in the probabilities estimated using both approaches. In the scenario analysis, transition probabilities derived from Weibull regression were changed with the age-dependent transition probabilities if a large discrepancy was found between probabilities estimated from Weibull regression and ONS.

***Costs***

One-way sensitivity analyses were carried out on each of the unit costs used to generate the total costs. Each unit cost derived from England NHS reference cost was varied around its interquartile ranges. Only one unit cost was varied individually each time and its influence on the NMB was calculated.

***Utilities***

Utilities derived from the study of Prescott *et al.* (2007) (1), Fallowfield *et al*. (1994) (285), and Peasgood *et al*. (2010)(2), including progression-free state within one year for surgery was changed around their 95%CI. Each coefficient used to predict the utilities related to the metastatic states, including types of treatments, type of response, the respondent, and the valuation method was also changed around its confidence interval. One-way sensitivity analysis was conducted using Microsoft Excel 2010.

## 4.4. Results

### 4.4.1. Transition probabilities

The annual transition probability (in each cycle) estimated by Weibull regression based on the cohort study (Chapter 2) showed that for patients who received surgery, there was a gradual increase in the yearly transition probabilities to first events, including transition from progression free to LR (0.003 in the first cycle to 0.026 in the 30th cycle),metastatic progression (0.004 in the first cycle to 0.025 in the 30th cycle), or death (0.006 in the first cycle to 0.046 in the 30th cycle). However, transition probabilities from LR to metastatic progression have largely increased from 0.000001 in the first cycle to 0.075 in the 30th cycle. Transition probabilities from LR to death have decreased from 0.00026 in the first cycle to 0.05 in the 30th cycle (Table 4.10.).

For patients who received PETx, there was a gradual increase in the yearly transition probabilities regarding transition from progression-free to LR (0.07 in the first cycle to 0.54 in the 30th cycle), metastatic progression (0.009 in the first cycle to 0.029 in the 30th cycle), or death (0.024 in the first cycle to 0.041 in the 30th cycle). However, there was a gradual decrease (0.049 in the first cycle to 0.028 in the 30th cycle) in transition probabilities from local recurrence to metastatic progression. (Table 4.11.). There was a large increase (0.0002 in the first cycle to 0.19 in the 30th cycle) in transition probabilities from local recurrence to death.

**Table 4.10. Yearly transition probabilities for patients who undergo surgery**

| From / To / Cycle /year | PF LR | PF MTST | PF Death | PF PF | LR LR | LR MTST | LR Death | LR PF | MTST MTST | MTST Death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.003 | 0.004 | 0.006 | 0.988 | 0.000 | 0.000 | 0.000 | 1.000 | 0.994 | 0.006 |
| 2 | 0.005 | 0.007 | 0.010 | 0.978 | 0.000 | 0.000 | 0.001 | 0.999 | 0.978 | 0.022 |
| 3 | 0.007 | 0.008 | 0.014 | 0.971 | 0.000 | 0.000 | 0.002 | 0.998 | 0.958 | 0.042 |
| 4 | 0.008 | 0.010 | 0.016 | 0.966 | 0.000 | 0.000 | 0.003 | 0.997 | 0.935 | 0.065 |
| 5 | 0.009 | 0.011 | 0.018 | 0.962 | 0.000 | 0.000 | 0.004 | 0.995 | 0.911 | 0.089 |
| 6 | 0.010 | 0.012 | 0.020 | 0.958 | 0.000 | 0.001 | 0.005 | 0.994 | 0.886 | 0.114 |
| 7 | 0.011 | 0.013 | 0.022 | 0.954 | 0.000 | 0.001 | 0.007 | 0.992 | 0.861 | 0.139 |
| 8 | 0.012 | 0.014 | 0.023 | 0.951 | 0.000 | 0.001 | 0.008 | 0.991 | 0.835 | 0.165 |
| 9 | 0.013 | 0.014 | 0.025 | 0.948 | 0.000 | 0.002 | 0.010 | 0.989 | 0.809 | 0.191 |
| 10 | 0.014 | 0.015 | 0.026 | 0.945 | 0.000 | 0.003 | 0.011 | 0.986 | 0.783 | 0.217 |
| 11 | 0.014 | 0.016 | 0.027 | 0.942 | 0.000 | 0.003 | 0.013 | 0.984 | 0.757 | 0.243 |
| 12 | 0.015 | 0.016 | 0.029 | 0.940 | 0.000 | 0.004 | 0.014 | 0.982 | 0.731 | 0.269 |
| 13 | 0.016 | 0.017 | 0.030 | 0.937 | 0.000 | 0.006 | 0.016 | 0.979 | 0.705 | 0.295 |
| 14 | 0.017 | 0.018 | 0.031 | 0.935 | 0.000 | 0.007 | 0.017 | 0.976 | 0.680 | 0.320 |
| 15 | 0.017 | 0.018 | 0.032 | 0.932 | 0.000 | 0.008 | 0.019 | 0.973 | 0.655 | 0.345 |
| 16 | 0.018 | 0.019 | 0.033 | 0.930 | 0.000 | 0.010 | 0.021 | 0.969 | 0.630 | 0.370 |
| 17 | 0.018 | 0.019 | 0.034 | 0.928 | 0.000 | 0.012 | 0.022 | 0.966 | 0.606 | 0.394 |
| 18 | 0.019 | 0.020 | 0.035 | 0.926 | 0.000 | 0.014 | 0.024 | 0.962 | 0.582 | 0.418 |
| 19 | 0.020 | 0.020 | 0.036 | 0.924 | 0.000 | 0.017 | 0.026 | 0.957 | 0.559 | 0.441 |
| 20 | 0.020 | 0.021 | 0.037 | 0.922 | 0.000 | 0.019 | 0.028 | 0.953 | 0.537 | 0.463 |
| 21 | 0.021 | 0.021 | 0.038 | 0.920 | 0.000 | 0.022 | 0.030 | 0.948 | 0.515 | 0.485 |
| 22 | 0.021 | 0.022 | 0.039 | 0.918 | 0.000 | 0.025 | 0.031 | 0.943 | 0.493 | 0.507 |
| 23 | 0.022 | 0.022 | 0.040 | 0.916 | 0.000 | 0.029 | 0.033 | 0.938 | 0.473 | 0.527 |
| 24 | 0.022 | 0.022 | 0.041 | 0.915 | 0.000 | 0.032 | 0.035 | 0.932 | 0.452 | 0.548 |
| 25 | 0.023 | 0.023 | 0.042 | 0.913 | 0.000 | 0.036 | 0.037 | 0.927 | 0.433 | 0.567 |
| 26 | 0.023 | 0.023 | 0.042 | 0.911 | 0.000 | 0.040 | 0.039 | 0.920 | 0.414 | 0.586 |
| 27 | 0.024 | 0.024 | 0.043 | 0.909 | 0.000 | 0.045 | 0.041 | 0.914 | 0.396 | 0.604 |
| 28 | 0.024 | 0.024 | 0.044 | 0.908 | 0.000 | 0.050 | 0.043 | 0.907 | 0.378 | 0.622 |
| 29 | 0.025 | 0.024 | 0.045 | 0.906 | 0.000 | 0.055 | 0.045 | 0.900 | 0.361 | 0.639 |
| 30 | 0.025 | 0.025 | 0.046 | 0.904 | 0.000 | 0.060 | 0.047 | 0.893 | 0.345 | 0.655 |
| 31 | 0.026 | 0.025 | 0.046 | 0.903 | 0.000 | 0.066 | 0.049 | 0.885 | 0.329 | 0.671 |
| 32 | 0.026 | 0.025 | 0.047 | 0.901 | 0.000 | 0.072 | 0.051 | 0.877 | 0.313 | 0.687 |

**(Note)** PF: progression free; LR: local recurrence; MTST: metastasis

**Table 4.11. Yearly transition probabilities for patients who receive primary endocrine therapy**

| From /To Cycle /year | PF LR | PF MTST | PF Death | PF PF | LR LR | LR MTST | LR Death | LR PF | MTST MTST | MTST Death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.077 | 0.009 | 0.024 | 0.890 | 0.030 | 0.049 | 0.000 | 0.921 | 0.986 | 0.014 |
| 2 | 0.141 | 0.012 | 0.028 | 0.819 | 0.077 | 0.041 | 0.001 | 0.881 | 0.926 | 0.074 |
| 3 | 0.181 | 0.014 | 0.030 | 0.775 | 0.117 | 0.039 | 0.003 | 0.841 | 0.835 | 0.165 |
| 4 | 0.213 | 0.016 | 0.031 | 0.740 | 0.154 | 0.037 | 0.005 | 0.804 | 0.727 | 0.273 |
| 5 | 0.239 | 0.017 | 0.032 | 0.712 | 0.187 | 0.036 | 0.008 | 0.769 | 0.613 | 0.387 |
| 6 | 0.262 | 0.018 | 0.033 | 0.687 | 0.218 | 0.035 | 0.011 | 0.736 | 0.501 | 0.499 |
| 7 | 0.283 | 0.019 | 0.034 | 0.665 | 0.248 | 0.034 | 0.014 | 0.704 | 0.399 | 0.601 |
| 8 | 0.301 | 0.019 | 0.034 | 0.645 | 0.275 | 0.034 | 0.018 | 0.673 | 0.310 | 0.690 |
| 9 | 0.318 | 0.020 | 0.035 | 0.627 | 0.301 | 0.033 | 0.023 | 0.643 | 0.234 | 0.766 |
| 10 | 0.334 | 0.021 | 0.035 | 0.610 | 0.326 | 0.033 | 0.027 | 0.614 | 0.173 | 0.827 |
| 11 | 0.349 | 0.021 | 0.036 | 0.595 | 0.350 | 0.032 | 0.032 | 0.586 | 0.125 | 0.875 |
| 12 | 0.362 | 0.022 | 0.036 | 0.580 | 0.372 | 0.032 | 0.037 | 0.558 | 0.088 | 0.912 |
| 13 | 0.375 | 0.022 | 0.036 | 0.566 | 0.394 | 0.032 | 0.043 | 0.532 | 0.060 | 0.940 |
| 14 | 0.387 | 0.023 | 0.037 | 0.553 | 0.414 | 0.032 | 0.049 | 0.505 | 0.041 | 0.959 |
| 15 | 0.399 | 0.023 | 0.037 | 0.541 | 0.434 | 0.031 | 0.055 | 0.480 | 0.027 | 0.973 |
| 16 | 0.410 | 0.024 | 0.037 | 0.529 | 0.452 | 0.031 | 0.062 | 0.455 | 0.017 | 0.983 |
| 17 | 0.420 | 0.024 | 0.038 | 0.518 | 0.470 | 0.031 | 0.068 | 0.431 | 0.011 | 0.989 |
| 18 | 0.430 | 0.025 | 0.038 | 0.508 | 0.488 | 0.031 | 0.075 | 0.407 | 0.007 | 0.993 |
| 19 | 0.439 | 0.025 | 0.038 | 0.497 | 0.504 | 0.030 | 0.082 | 0.383 | 0.004 | 0.996 |
| 20 | 0.449 | 0.025 | 0.038 | 0.488 | 0.520 | 0.030 | 0.090 | 0.360 | 0.002 | 0.998 |
| 21 | 0.457 | 0.026 | 0.039 | 0.478 | 0.535 | 0.030 | 0.098 | 0.337 | 0.001 | 0.999 |
| 22 | 0.466 | 0.026 | 0.039 | 0.469 | 0.550 | 0.030 | 0.105 | 0.315 | 0.001 | 0.999 |
| 23 | 0.474 | 0.026 | 0.039 | 0.461 | 0.564 | 0.030 | 0.113 | 0.293 | 0.000 | 1.000 |
| 24 | 0.482 | 0.027 | 0.039 | 0.452 | 0.578 | 0.029 | 0.122 | 0.271 | 0.000 | 1.000 |
| 25 | 0.489 | 0.027 | 0.039 | 0.444 | 0.591 | 0.029 | 0.130 | 0.250 | 0.000 | 1.000 |
| 26 | 0.497 | 0.027 | 0.040 | 0.437 | 0.603 | 0.029 | 0.138 | 0.229 | 0.000 | 1.000 |
| 27 | 0.504 | 0.028 | 0.040 | 0.429 | 0.616 | 0.029 | 0.147 | 0.208 | 0.000 | 1.000 |
| 28 | 0.510 | 0.028 | 0.040 | 0.422 | 0.627 | 0.029 | 0.156 | 0.188 | 0.000 | 1.000 |
| 29 | 0.517 | 0.028 | 0.040 | 0.415 | 0.639 | 0.029 | 0.165 | 0.168 | 0.000 | 1.000 |
| 30 | 0.524 | 0.028 | 0.040 | 0.408 | 0.650 | 0.029 | 0.174 | 0.148 | 0.000 | 1.000 |
| 31 | 0.530 | 0.029 | 0.040 | 0.401 | 0.660 | 0.029 | 0.183 | 0.128 | 0.000 | 1.000 |
| 32 | 0.536 | 0.029 | 0.041 | 0.395 | 0.670 | 0.028 | 0.193 | 0.109 | 0.000 | 1.000 |

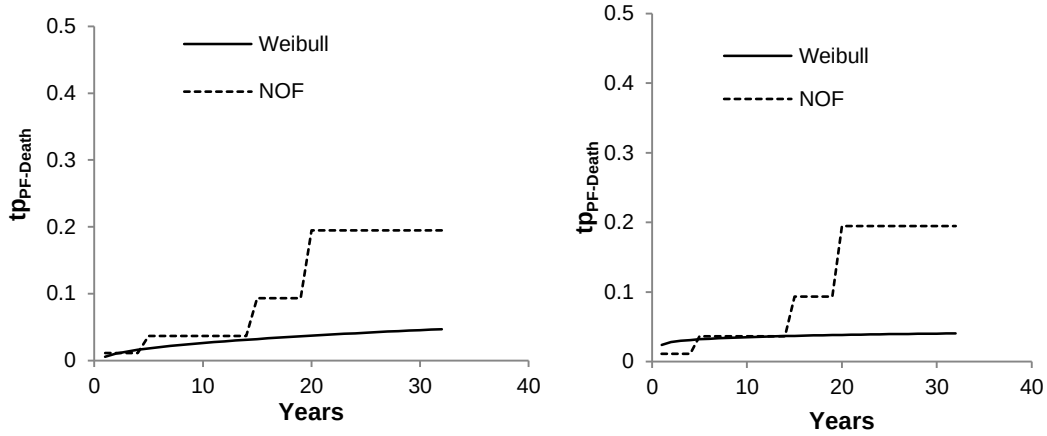
**(Note)** PF: progression free; LR: local recurrence; MTST: metastasis

There are higher overall mortality rates in the sample dataset derived from Weibull model compared with the general population when transition occurred from progression-free, LR, or metastasis to death in the surgical and PETx group. Thus, those six transition probabilities were changed using scenario sensitivity analysis in order to examine whether using the national life table probabilities would change the treatment selection (Figure 4.3.).

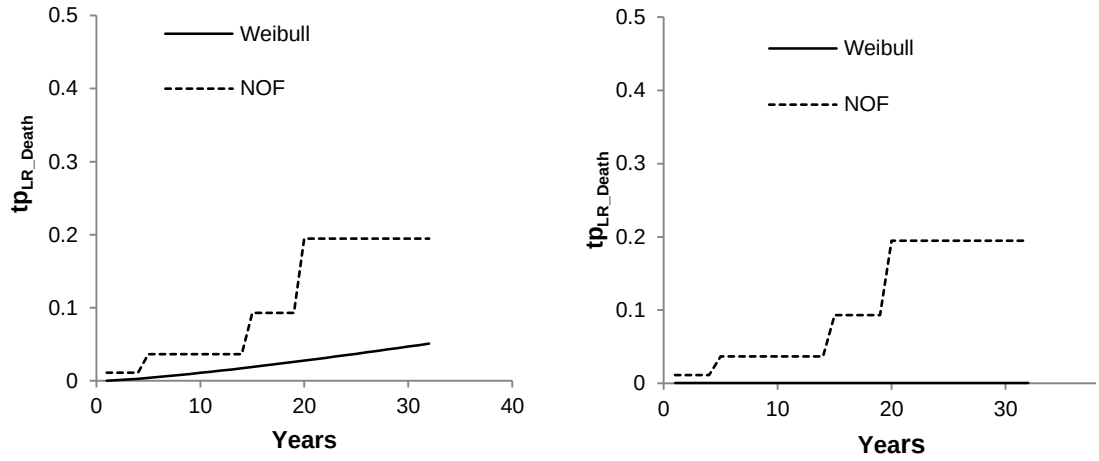
**Figure 4.3. Transition probabilities estimated using different approaches, including parametric regression and life table**

**(a) Surgery** **(b) PETx**

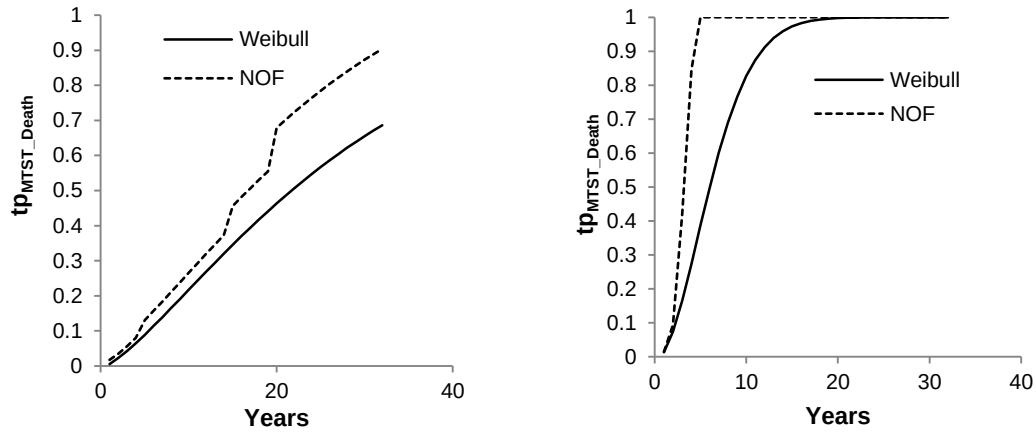
***Transition probabilities from progression free to death***




***Transition probabilities from local recurrence to death***




***Transition probabilities from metastasis to death***




**(Note)** $tp_{PF\text{-}Death}$: transition probabilities from progression free to death; $tp_{LR\text{-}Death}$: transition probabilities from local recurrence to death; $tp_{MTST\text{-}Death}$: transition probabilities from metastasis to death NOF: national life table

### 4.4.2. Cost associated with different disease states

The annual transition costs (in each cycle) for each transition state estimated based on the cohort study (Chapter 2) showed that the costs associated with the progression-free state for patients who received surgery within the first year were higher compared with patients who received PETx. However, the costs in subsequent years were lower in the surgical group compared with the PETx group (Table 4.12., Table 4.13., Table 4.14.). Furthermore, the costs associated with the locoregional progression state following PETx within the first and following years were higher than those of the surgical group. The costs associated with the metastatic state following surgery were quite similar with the PETx group (Table 4.15., Table 4.16.).

**Table 4.12. Costs associated with the progression-free state within the first year**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***Surgery*** | | | | |
| *WLE* | 1.00 | 2635.00 | 1212.10 | 0.46 |
| *Mastectomy* | 1.00 | 2635.00 | 1370.20 | 0.52 |
| *Mastectomy+axillary clearance* | 1.00 | 3398.77 | 67.98 | 0.02 |
| *Axillary clearance* | 1.00 | 2481.01 | 744.30 | 0.30 |
| *Excess bed days* | (bed days) | | | |
| *WLE* | 3.00 | 373.00 | 514.74 | 0.46 |
| *Mastectomy* | 5.00 | 373.00 | 969.80 | 0.52 |
| *Mastectomy+axillary clearance* | 4.00 | 348.00 | 27.84 | 0.02 |
| ***Adjuvant therapy*** | | | | |
| ***ETx*** | | | | |
| *Tamoxifen* | 12.16 | 2.27 | 17.11 | 0.62 |
| *Anastrazole* | 13.03 | 68.56 | 303.73 | 0.34 |
| *Letrozole* | 13.03 | 3.32 | 0.13 | 0.00 |
| *Faslodex* | 13.00 | 522.41 | 20.37 | 0.00 |
| ***RTx*** | | | | |
| *Delivery of RTx* | *15.00* | 126.00 | 680.40 | 0.36 |
| *Planning of RTx* | 1.00 | 796.90 | 87.66 | 0.11 |
| ***Follow-up*** | | | | |
| *1 year* | 1.00 | 119.00 | 119.00 | 1.00 |
| Sum | | | 6135.37 | |
| **PETx as an initial treatment** | | | | |
| ***PETx*** | (Pack) | | | |
| *Tamoxifen* | 12.17 | 2.27 | 16.29 | 0.59 |
| *Anastrazole* | 13.04 | 68.56 | 303.87 | 0.34 |
| *Tamoxifen+Anastrazole* | 12.17 for Tamoxifen<br>13.04 for Anastrazole | 2.27<br>68.56 | 64.49 | 0.07 |
| ***Follow-up*** | | | | |
| *1 year* | 3.00 | 119.00 | 357.00 | |
| Sum | | | 741.66 | |

**(Note)** PETx: primary endocrine therapy; ETx: endocrine therapy; RTx: radiotherapy

**Table 4.13. Costs associated with the progression-free state between two to five years**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***Adjuvant therapy*** | (Pack) | | | |
| *Tamoxifen* | 12.17 | 2.27 | 10.22 | 0.37 |
| *Anastrazole* | 13.03 | 68.56 | 80.40 | 0.09 |
| *Letrozole* | 13.03 | 3.32 | 0.13 | 0.00 |
| *Faslodex* | 12.00 | 522.41 | 18.81 | 0.00 |
| *Tamoxifen+ Anastrazole* | 12.17 for Tamoxifen 13.04 for Anastrazole | 2.27 68.56 | 32.88 | 0.25 |
| ***Follow-up*** | | | | |
| *> 1 year* | 1.00 | 119.00 | 119.00 | 1.00 |
| Sum | | | 261.43 | |
| **PETx as an initial treatment** | | | | |
| ***Adjuvant therapy*** | (Pack) | | | |
| *Tamoxifen* | 12.17 | 2.27 | 16.29 | 0.59 |
| *Anastrazole* | 13.04 | 68.56 | 303.87 | 0.34 |
| *Tamoxifen+ Anastrazole* | 12.17 for Tamoxifen 13.04 for Anastrazole | 2.27 68.56 | 64.49 | 0.07 |
| ***Follow-up*** | | | | |
| *> 1 year* | 2.00 | 119.00 | 238.00 | 1.00 |
| Sum | | | 622.66 | |

**(Note)** PETx: primary endocrine therapy; ETx: endocrine therapy

**Table 4.14. Costs associated with the progression-free state over five years**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***Follow-up*** | 1.00 | 119.00 | 119.00 | 1.00 |
| Sum | | | 119.00 | |
| **PETx as an initial treatment** | | | | |
| *PETx* | (Pack) | | | |
| *Tamoxifen* | 12.17 | 2.27 | 16.29 | 0.59 |
| *Anastrazole* | 13.04 | 68.56 | 303.87 | 0.34 |
| *Tamoxifen+ Anastrazole* | 12.17 for Tamoxifen 13.04 for Anastrazole | 2.27 68.56 | 64.49 | 0.07 |
| ***Follow-up*** | | | | |
| *> 1 year* | 2.00 | 119.00 | 238.00 | 1.00 |
| Sum | | | 622.66 | |

**Table 4.15. Costs associated with the locoregional progression state within the first year**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| *Mastectomy* | 1.00 | 2635.00 | 158.10 | 0.06 |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 64.84 | 0.06 |
| *Tamoxifen* | 12.17 | 2.27 | 5.25 | 0.19 |
| *Anastrazole* | 13.03 | 68.56 | 607.47 | 0.68 |
| ***Follow-up*** | | | | |
| *Surgery* | 1.00 | 119.00 | 7.14 | 0.06 |
| *Non-surgery* | 3.00 | 119.00 | 335.58 | 0.94 |
| **New admission** | 1.00 | 169.00 | 169.00 | 1.00 |
| **MDT** | 1.00 | 86.00 | 86.00 | 1.00 |
| **CT scan** | 1.00 | 129.00 | 129.00 | 1.00 |
| Sum | | | 1562.38 | |
| **PETx as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| *Mastectomy* | 1.00 | 2635.00 | 105.40 | 0.04 |
| ***ETx*** | | | | |
| *Megacetrol* | 12.17 | 19.52 | 4.75 | 0.02 |
| *Tamoxifen* | 12.17 | 2.27 | 1.93 | 0.07 |
| *Exemestane* | 12.17 | 88.80 | 259.37 | 0.24 |
| *Anastrazole* | 13.03 | 68.56 | 544.94 | 0.61 |
| ***RTx*** | | | | |
| *Delivery of RT x* | 15.00 | 126.00 | 18.90 | 0.01 |
| *Planning of RTx* | 1.00 | 796.90 | 7.97 | 0.01 |
| ***Follow-up*** | | | | |
| *Surgery* | 1.00 | 119.00 | 4.76 | 0.04 |
| *Non-surgery* | 3.00 | 119.00 | 342.72 | 0.96 |
| **New admission** | 1.00 | 169.00 | 169.00 | 1.00 |
| **MDT** | 1.00 | 86.00 | 86.00 | 1.00 |
| **CT scan** | 1.00 | 129.00 | 129.00 | 1.00 |
| Sum | | | 1674.74 | |

**(Note)** ETx: endocrine therapy; CT: Computerised Tomography; RTx: radiotherapy; MDT: Multidisciplinary Team

**Table 4.16. Costs associated with the locoregional progression state over one year**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 64.84 | 0.06 |
| *Megacetrol* | 12.17 | 19.52 | 0.00 | |
| *Tamoxifen* | 12.17 | 2.27 | 5.25 | 0.19 |
| *Anastrazole* | 13.03 | 68.56 | 607.47 | 0.68 |
| ***Follow-up*** | | | | |
| *Surgery* | 1.00 | 119.00 | 7.14 | 0.06 |
| *Non-surgery* | 2.00 | 119.00 | 223.72 | 0.94 |
| Sum | | | 908.42 | |
| **PETx as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 259.37 | 0.24 |
| *Megacetrol* | 12.17 | 19.52 | 4.75 | 0.02 |
| *Tamoxifen* | 12.17 | 2.27 | 1.93 | 0.07 |
| *Anastrazole* | 13.03 | 68.56 | 544.94 | 0.61 |
| ***Follow-up*** | | | | |
| *Surgery* | 1.00 | 119.00 | 4.76 | 0.04 |
| *Non-surgery* | 2.00 | 119.00 | 228.48 | 0.96 |
| Sum | | | 1044.23 | |

**(Note)** ETx: endocrine therapy; PETx: primary endocrine therapy

**Table 4.17. Costs associated with the metastatic progression state within one year**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 961.82 | 0.89 |
| ***Follow-up*** | | | | |
| *Non-surgery* | 3.00 | 119.00 | 357.00 | 1.00 |
| **New admission** | 1.00 | 169.00 | 169.00 | 1.00 |
| **MDT** | 1.00 | 86.00 | 86.00 | 1.00 |
| **CT scan** | 1.00 | 129.00 | 129.00 | 1.00 |
| Sum | | | 1702.82 | |
| **PETx as an initial treatment** | | | | |
| **2nd line treatment** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 335.02 | 0.31 |
| *Faslodex* | 12.00 | 522.41 | 501.51 | 0.08 |
| *Anastrazole* | 12.17 | 19.52 | 128.28 | 0.54 |
| ***Follow-up*** | | | | |
| *Non-surgery* | 3.00 | 119.00 | 357.00 | 1.00 |
| **New admission** | 1.00 | 169.00 | 169.00 | 1.00 |
| **MDT** | 1.00 | 86.00 | 86.00 | 1.00 |
| **CT scan** | 1.00 | 129.00 | 129.00 | 1.00 |
| Sum | | | 1705.81 | |

**(Note)** ETx: endocrine therapy; CT: Computerised Tomography; RTx: radiotherapy; MDT: Multidisciplinary Team

**Table 4.18. Costs associated with the metastatic progression state over one year**

| Resource | Frequency | Unit costs | Cycle length cost | Proportion of patients |
|---|---|---|---|---|
| **Surgery as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 961.82 | 0.89 |
| ***Follow-up*** | | | | |
| *Non-surgery* | 2.00 | 119.00 | 238.00 | 1.00 |
| Sum | | | 1199.82 | |
| **PETx as an initial treatment** | | | | |
| ***2nd line treatment*** | | | | |
| ***ETx*** | | | | |
| *Exemestane* | 12.17 | 88.80 | 335.02 | 0.31 |
| *Faslodex* | 12.00 | 522.41 | 501.51 | 0.08 |
| *Anastrazole* | 12.17 | 19.52 | 128.28 | 0.54 |
| ***Follow-up*** | | | | |
| *Non-surgery* | 2.00 | 119.00 | 238.00 | 1.00 |
| Sum | | | 1202.81 | |

**(Note)** ETx: endocrine therapy; PETx: primary endocrine therapy

### 4.4.3. Cost-effectiveness analysis

PETx was associated with lower costs (Incremental costs: -£364.21), lower LYGs (incremental LYGs: -2.26) and QALYs (incremental QALYs: -1.87) compared with surgery (Table 4.19.). In the subgroup analysis, PETx was associated with higher costs (incremental costs: £1043.15), lower LYGs (incremental LYGs: -0.95) and QALYs (incremental QALYs: -0.56) compared with surgery (Table 4.19.).

**Table 4.19. Deterministic results for both base case and subgroup analyses**

| | **Base case analysis** | | **Subgroup analysis (H-score over 250)** | |
|---|---|---|---|---|
| | **Surgery** | **PETx** | **Surgery** | **PETx** |
| **Mean LYGs per patient** | 13.38 | 10.76 | 13.44 | 12.49 |
| **Mean QALYs per patient** | 10.68 | 8.81 | 10.78 | 10.22 |
| **Mean costs per patient** | 8767.77 | 8403.56 | 8585.53 | 9628.68 |
| **Incremental LYGs** | -2.62 | | -0.95 | |
| **Incremental QALYs** | -1.87 | | -0.56 | |
| **Incremental costs** | -364.21 | | 1043.15 | |
| **Mean ICER** | 138.96 | | -1094.36 | |
| **Mean ICUR** | 194.72 | | -1849.43 | |

**(Note)** LYGs: life year gained; QALYs: quality-adjusted life-year; PETx: primary endocrine therapy; ICER: incremental cost-utility ratio; ICUR: incremental cost-effectiveness ratio

### 4.4.4. Probabilistic sensitivity analysis

The cost of PETx is significantly lower than surgery. The incremental mean cost was -£821.47 (95%CI: -866.90, -776.04), with LYG difference was –2.26 (95%CI: -2.32, -2.2), and QALY difference of -1.61 (95%CI: -1.65, -1.54) (Table 4.20.).

The probability of PETx being cost-effective at WTA of £21,000 per QALY was 24% (Figure 4.5.). ICUR was -£514.61 per QALY, 95%CI: (-7106.1, 8307.3) (Table 4.20.). The majorities of the ICUR point estimates distributed in the NW (54.67%) and SW (37.49%) quadrants (Figure 4.4.)

The subgroup analysis, the incremental mean cost for PETx was significantly higher than surgery and the incremental mean cost was £351.42 (95%CI: 302.69, 400.15), LYG difference was -0.9 (95%CI: -0.96, -0.84) and QALY difference was -0.57 (95%CI: -0.62, -0.52) (Table 4.20.).

The probability of PETx being cost-effective at WTA of £21,000 per QALY was 43% (Figure 4.5.). ICUR was -£618.07 per QALY, 95%CI:(-8,575.87, 10,094.38) (Table 4.20.). The majorities of the ICUR point estimates distributed in the NE (38.28%) and SW (34.79%) quadrants (Figure 4.4.).

**Table 4.20. Probabilistic sensitivity results for both base case and subgroup analyses**

| | Base case analysis | | Subgroup analysis (H-score over 250) | |
|---|---|---|---|---|
| | **Surgery (n=10000)** | **PETx (n=10000)** | **Surgery (n=10000)** | **PETx (n=10000)** |
| **Disaggregate results** | | | | |
| Mean LYGs per patient (95%CI) | 12.66 (9.75, 15.18) | 10.4 (3.93, 14.47) | 12.65 (9.06, 15.82) | 11.75 (4.59, 15.75) |
| Mean QALYs per patient (95%CI) | 10.05 (7.66, 12.23) | 8.46 (3.27, 11.91) | 10.11 (7.17, 12.77) | 9.54 (3.8, 12.9) |
| Mean costs per patient (95%CI) | 9001.31 (7103.26, 11223.81) | 8179.84 (3053.67, 11791.69) | 8767.16 (6861.25, 10976.94) | 9118.58 (3408.3, 12975.51) |
| **Incremental results** | | | | |
| Incremental LYGs (95%CI) | -2.26 (-2.32, -2.2) | | -0.9 (-0.96, -0.84) | |
| Incremental QALYs (95%CI) | -1.6 (-1.65, -1.54) | | -0.57 (-0.62, -0.52) | |
| Incremental costs (95%CI) | -821.47 (-866.90,-776.04) | | 351.42 (302.69, 400.15) | |
| **Aggregate results** | | | | |
| Mean ICER (95%CI) | 363.3 (-6014.99, 5756.15) | | -390.67 (-7295.41, 7776.54) | |
| Mean ICUR (95%CI) | 514.61 (-7106.1, 8307.3) | | -618.07(-8575.87, 10094.38) | |
| **Percentages of ICUR in each quadrant (95%CI)** | | | | |
| SE | 6.33 | | 5.98 | |
| NE | 19.41 | | 38.28 | |
| SW | 56.17 | | 34.79 | |
| NW | 18.09 | | 20.95 | |

**(Note)** PETx: primary endocrine therapy; LYGs: life year gained; QALYs: quality-adjusted-life year; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; SE: southeast; NE: northeast; SW: southwest; NW: northwest; CI: confidence interval

**Figure 4.4. Cost effectiveness plan for base case and subgroup analyses of H-score over 250**

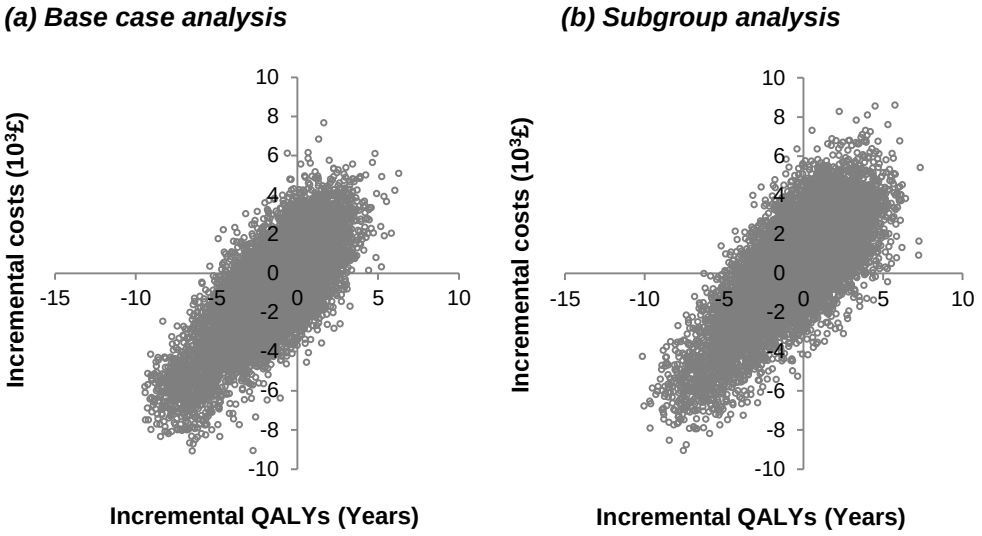
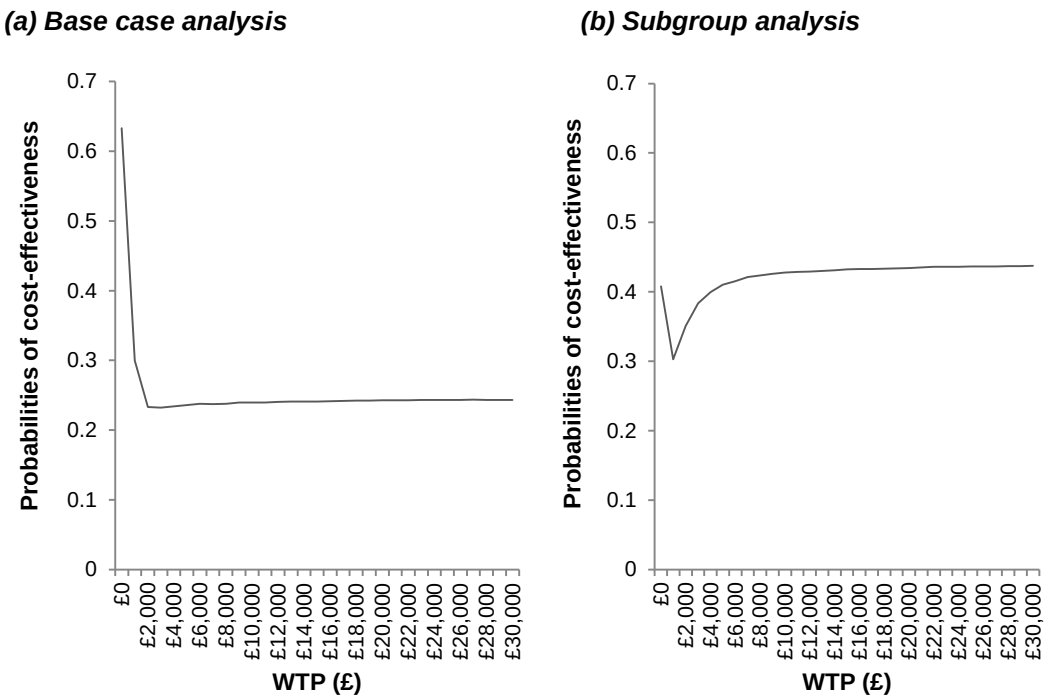



**Figure 4.5. Cost-effectiveness acceptability curve for base case and subgroup analyses of H-score over 250 for cost-utility analysis**



### 4.4.5. Sensitivity analysis

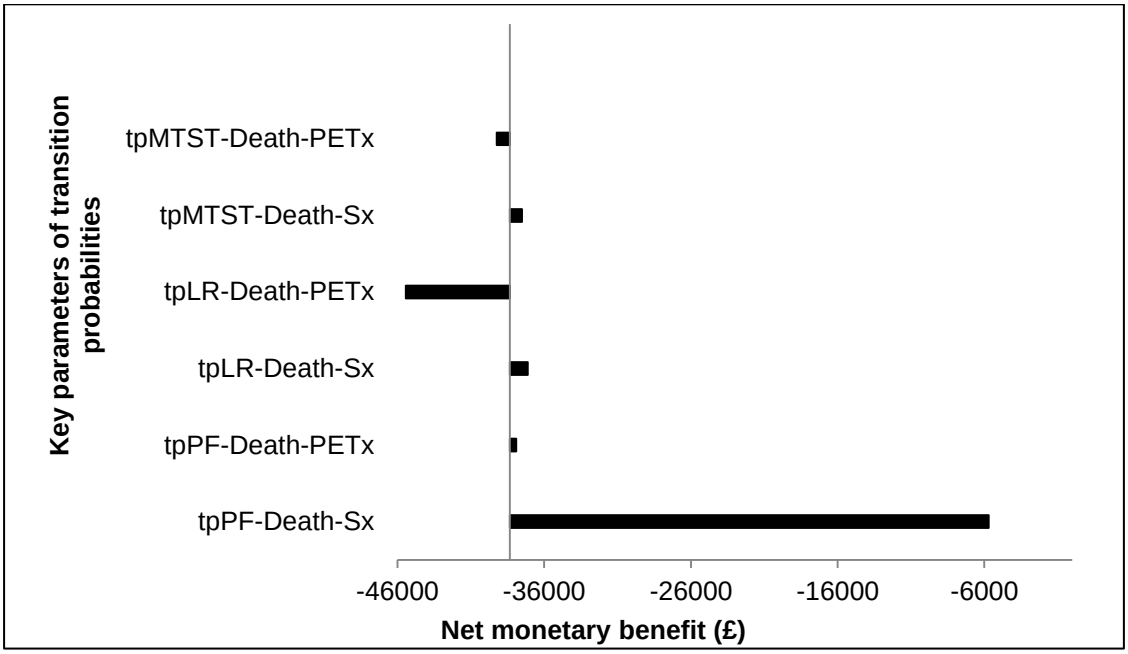
The NMB for PETx compared to surgery at a WTA of £21,000 was -38,342.86, i.e. this implies that if the decision-maker is willing to accept £21,000 reduction in costs for each QALY loss, the costs forgone from adopting PETx is higher by £38,342.86.

Using age-dependent mortality estimated from the ONS and changing the costs and utility around their interquartile range or 95%CI did not change the decision of treatment selection, i.e. the NMB remained less than zero.

***Varying transition probabilities in scenario analysis***

Although using probabilities from the national life table did not change the treatment selection, using the ONS probabilities for transition from progression-free to death in the surgical groups resulted in lower NMB loss as compared to the base case (Figure 4.6.).

**Figure 4.6. Scenario analysis for changing probabilities to death based on office national statistics**

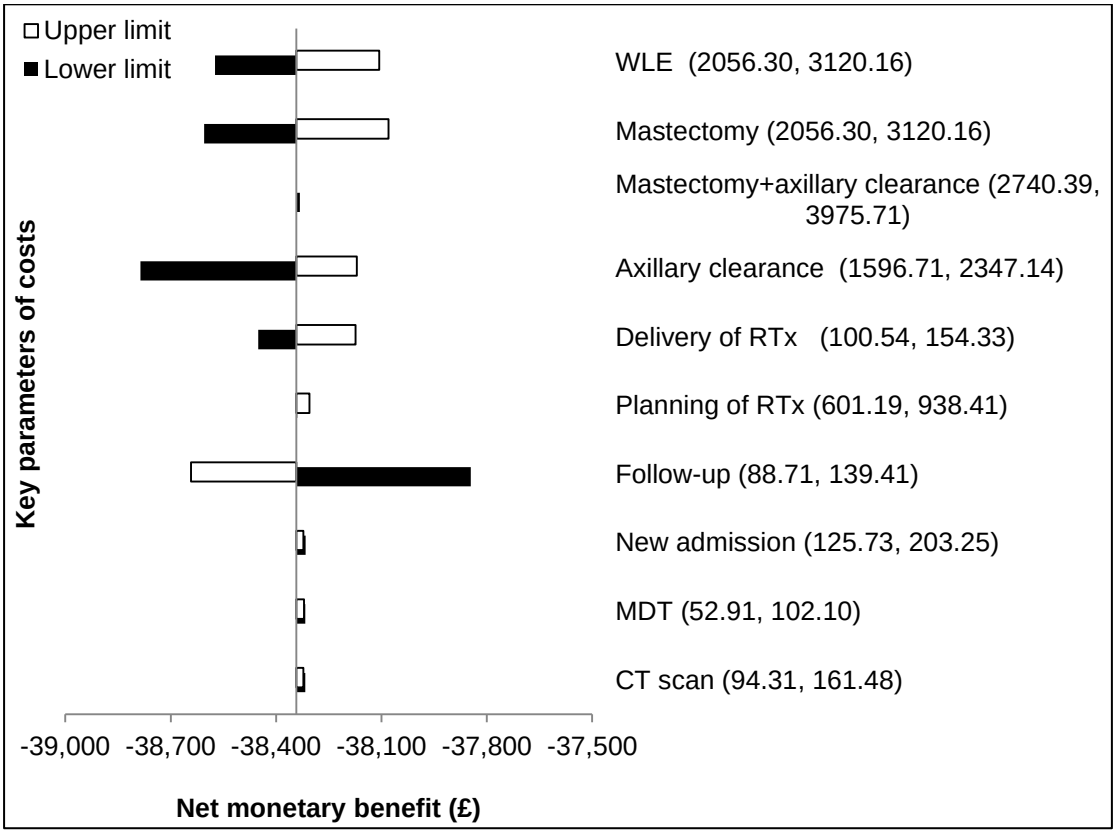



**(Note)** $tp_{LR\text{-}Death\text{-}PETx}$: transition probabilities from progression-free to death for primary endocrine therapy group; $tp_{PF\text{-}Death\text{-}PETx}$: transition probabilities from progression-free to death for primary endocrine therapy; $tp_{LR\text{-}Death\text{-}Sx}$: transition probabilities from local recurrence to death for surgical group; $tp_{PF\text{-}Death\text{-}Sx}$: transition probabilities from progression-free to death for surgical group.

***Varying costs in one-way sensitivity analysis***

Although varying the individual unit cost used to generate the total costs for each health state did not result in a change of dominating treatment, varying the unit cost of WLE, mastectomy, and follow-up around their interquartile range demonstrated the greatest impacts on NMB values. Changing the mean unit cost values of WLE or mastectomy to their upper limits resulted in lower NMBs loss of -£38,106.45 and -£ 38,080.05 towards PETx (i.e. increasing the benefit of PETx over surgery), respectively, whereas varying the follow-up mean unit costs to their upper limit resulted in higher NMB loss of -£38,642.17. Changing the mean unit cost values of WLE and mastectomy to their lower limits resulted in higher NMBs loss of -£38,573.46 and -£38,604.95 (i.e. decreasing benefit of PETx over surgery), respectively, whereas varying the follow-up mean unit costs to their lower limit resulted in a lower NMB loss of -£37,845.80 (Figure 4.7.)

**Figure 4.7 Tornado diagram of individual unit cost used to estimate the total costs**



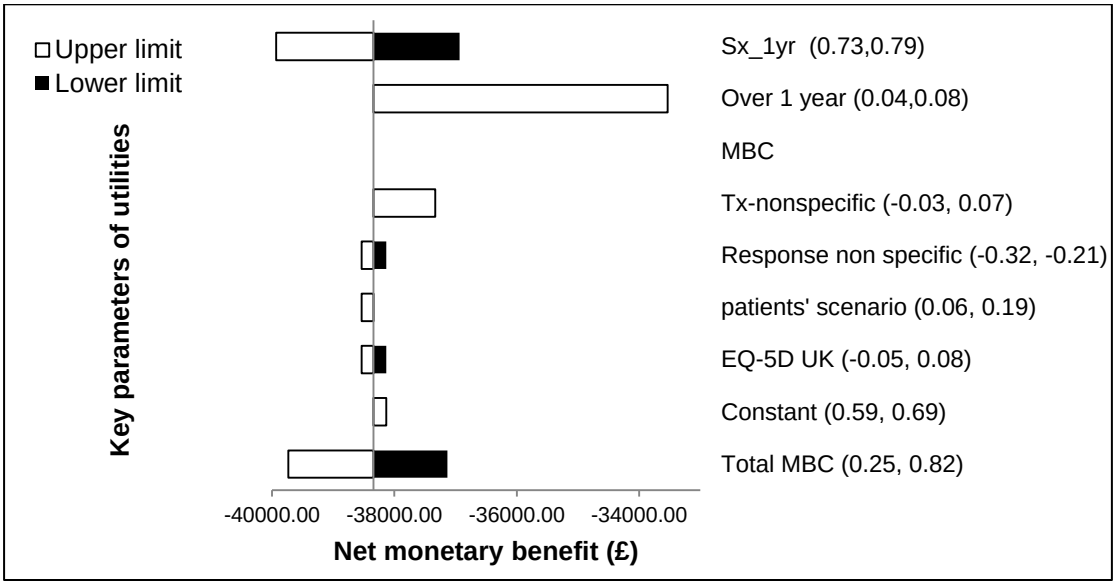

**(Note)** WLE: wide local excision; RTx: radiotherapy; MDT: multidisciplinary team; CT: computerised tomography; FEC: Fluorouracil (5FU), epirubicin and cyclophosphamide

***Varying utilities in one-way sensitivity analysis***

Although varying the individual utility components that were used to estimate the utilities of using PETx and surgery as initial treatments for different health states and different years did not result in a change in the treatment selection, varying the utility values of the progression-free states of surgery within one year demonstrated the greatest impacts on NMB values. Varying the utility value of surgery as an initial treatment to their upper limits resulted in higher NMB loss of -£39,933.72 towards PETx while varying the utility value of surgery to their lower limits resulted in lower NMB loss of -£36,933.72 towards PETx (

Figure 4.8).

**Figure 4.8 Tornado analysis of utility components used to estimate the utility values for both treatments**




**(Note)** Tx: treatment**;** PETx: primary endocrine therapy; Sx: surgery; MBC: metastatic breast cancer; UK: United Kingdom; EQ-5D: EQ-5D: European Quality of Life-5 Dimensions

## 4.5. Discussion

### 4.5.1. Main findings

This chapter used a decision analytical model to estimate and compare the lifetime costs of the secondary care and outcomes of receiving PETx as against surgery in older women with primary breast cancer. In addition, it is also considered as an early decision model in the economic evaluation iterative process (Section 4.5.6). The health states of the Markov model were designed based on the literature and expert opinion. The main health states for both treatment strategies were progression free, locoregional and metastatic progression, and death.

Deterministic and probabilistic results of the base case analysis showed that surgery was associated with longer LYGs, QALYs, and higher costs than PETx. The PSA analysis of the base case showed the probability of PETx being cost-effective compared with surgery was low. However, the subgroup analysis was associated with small difference in LYGs and QALYs in the both treatment groups, whilst PETx was associated with lower costs compared to surgery. The small difference in LYGs observed in patients with H-score who received surgery or PETx could be partly explained due to a non significant difference in breast cancer survival in patients with H-score over 250 who received PETx compared to those who received surgery. Thus, the estimation of the long-term effectiveness of both surgery and PETx might result in similar LYGs in both treatments or in the particular group of patients having H-score over 250. One-way and scenario sensitivity analysis demonstrated that the variation in model key parameters did not change the model's treatment selection.

There are some factors in this study related to the measures of effectiveness, costs, and utilities that may influence the cost-effectiveness results were discussed in the following sections.

### 4.5.2. Factors related to effectiveness measures

Although this economic model approach overcomes the issue of censoring by allowing all the patients to observe the final outcomes (i.e. death), the survival model that was used to extrapolate the survival time beyond the cohort follow-up time horizon was predicted based on age, clinical size and ER-positivity only. However, since other patients' characteristics, which may influence the specification of the model, were not accounted for in the model, insufficient prediction of the model could occur and may bias the estimation of the transition probabilities.

In addition, the survival model was calculated based on the time to the event, including time to progression and death recorded in the database. However, given that there were an under recording of the time to progression variables for the non-surgical treatments, which were imputed using regression models (Chapter 2), any bias in the imputation approach will influence the specification of the model, and consequently the estimated transition probabilities.

### 4.5.3. Factors related to resource use and costs

Patients who survive longer would consume more resources and costs, and thus any changes to survival times after extrapolation would be reflected on their associated costs. Therefore, any bias in the survival time results will be reflected in the cost results.

In addition, assumptions were made related to the cost of treating metastatic states. Since the actual resource use associated with treating metastasis were not fully recorded in the database, assumptions were made based on expert opinion (Chapter 2).

### 4.5.4. Factors related to utility

Few utility studies have been undertaken in older women with primary breast cancer. However, long-term utilities related to older women with metastasis or recurrence were not available, and thus assumptions were made to predict those utility values based on the younger population which may not represent the actual utility values incurred by older patients in different health states. Therefore, this would create more uncertainty around the utility values and thus, may bias the QALY results for both surgical and PETx group.

### 4.5.5. Cost-effectiveness threshold

NICE assigned a cost-effectiveness threshold to consider whether any health technology represents a good value for money. However, the cost-effectiveness threshold differs based on whether the new health technology associated with health gain or loss (318). WTP is considered when the health technology is associated with relative improvements in effectiveness at a higher cost, i.e. when the ICER is placed in the NE quadrant of the CEAC (318,319). However, WTA is considered when a health technology is associated with reduction in effectiveness and cost, i.e. ICER is placed in the SW quadrant (318,319).

Whereas NICE recommends a WTP threshold of £20,000-£30,000 per QALY for the reimbursement of a healthcare technology with higher effectiveness and costs, the WTA threshold recommended by NICE to be cost-effective because it is both less costly and less effective than current practice is still unclear (320,321).

The WTA for reduction in QALY is generally higher than the WTP for the gain in QALY, which implies that the slope of the WTA curve is steeper than in the WTP curve. This is explained by the fact that a greater amount of cost saving will be required to accept losing a QALY in the SW quadrant than the amount be paid to generate a QALY in the

NE quadrant since the 'selling price' of a QALY is higher than its 'buying price' (320). A review of NICE technology appraisal (TA) guidance documents showed that there is no evidence that NICE considers a WTA threshold in the SW that differs from the WTP in NE. However, based on available evidence, the NICE WTA threshold may be between £21,100 per QALY and £250,000 per QALY (321).

### 4.5.6. Future recommendations

Based on the existing evidence, the probability of PETx being cost-effective for the overall cohort was low compared with surgery. However, similar LYGs were observed in the subgroup analysis with H-score over 250 indicating that there is a potential for PETx to be cost-effective for this particular group of patients if further information in terms of patients' characteristics can be collected that reduces the bias towards surgery. Given the potential resource constraints in research funding, economic evaluation should follow an iterative process (i.e. conducting more future studies) as more evidence becomes available in order to reduce the uncertainty surrounding the cost-effectiveness estimates (322).

Iterative economic evaluation goes through five stages: it starts by 1) identifying the research problem, followed by 2) modelling based on the existing evidence, 3) setting research priorities, 4) conducting a research based on a primary trial, and 5) finally synthesising and modelling based on the updated evidence (233,322,323). Developing an early decision model based on the existing evidence (stage 2) allows a full quantification of the uncertainty surrounding the parameters and the results based on the model-type evaluation could be used to describe the value of future research needed to reduce the uncertainty surrounding the cost-effectiveness ratio, by estimating the value of information analysis, which would inform the appropriate research design (stage 3), and thus, this will help decision-makers to prioritise research funding based on their limited budget. Furthermore, identifying the parameters that

may have impact on the treatment research selection through the series of sensitivity analyses would enable designing studies with particular focus on reducing the uncertainty around these particular parameters (323).

The value of information analysis is based on the quantification of the costs of decision uncertainty in terms of forgone health and inefficient use of health care resources (173). Since there is a chance that a wrong decision will be made which is equal to one minus the probabilities of PETx being cost-effective, costs will be associated with this wrong decision (173). This is called the expected value of perfect information (EVPI) (i.e. one minus the probability of PETx being cost-effective), because perfect information can eliminate the possibility of making the wrong decision. In addition, the expected value of perfect information for parameters (EVPPI) can be used to identify the costs associated with surrounding parameters (or groups of parameters) in the decision model that have a greater impact on the cost-effectiveness, i.e. parameters may have considerable uncertainty and impact on the cost-effectiveness decision, indicating a need for further research in these specific parameters (173).

Since the probability of PETx being cost-effective was low, based on the economic model, there is more uncertainty about it is adoption, and thus, the expected cost and EVPI will be very high. Moreover, given that one-way sensitivity analysis showed that none of the parameters had an impact on changing the decision adoption based on the model results, assessing the values of EVPI for each parameter deemed unnecessary. Although the EVPI relating to model parameters explored in the PSA would be very high, the value of further research to resolve uncertainties relating to parameters or assumptions which were not quantified in the PSA is not known, and hence, the research problem (stage 1) is needed to be modified to consider other parameters or patients' characteristics that would influence the LYGs and costing results, i.e. additional future analysis of the cost-effectiveness of tamoxifen against

surgery in patients with ER-positive, adherent to ETx, and fit for surgery are needed. This could be obtained by searching for existing databases or cancer registries that could potentially provide long-term follow-up for older women with primary breast cancer, including the detailed recording of their treatment pathways, recording of adherence measures, frailty, ER status, and other comorbidities.

The availabilities of pre-existing data to populate the model would allow quantifying the uncertainty associated with wrong decisions and avoid conducting a costly and time-consuming primary research (i.e. RCT) for PETx if it has little chance of being cost-effective. Effectiveness and cost estimates derived from these databases will update the economic model (stage 4).

Although conducting a pragmatic RCT to provide the main source for economic evaluation is recommended (193), it is challenging to conduct an RCT in older women owing to poor recruitment, and thus, conducting a retrospective or prospective cohort based on an existing database would be more appropriate. The advantage that a pragmatic RCT offers over the experimental RCT is that it balances between the external and internal validity; it retains some of the RCTs features of being randomly allocated to treatments in order to minimise selection bias. However, it allows comparing of the commonly used treatments in current practice and follows the patients in real-life conditions, thus enhancing the generalisability to the clinical practice (160).

This iterative approach provides a framework in which evidence from different sources can be synthesised and updated with any data that emerges in order to reduce the uncertainty associated with the cost-effectiveness of a defined research question. Using a decision analytical model offers the advantage of incorporating trial-based

evidence in an iterative economic evaluation framework rather than using single trial-based economic evaluation, which fails to allow the iterative process (233,323).

### 4.5.7. Strengths and limitations

This is the first study conducted to investigate the cost-effectiveness of using PETx against surgery in older women based on a decision analytical model. The model was structured based on the systematic review of economic models and modified by treatment pathways based on the real-life cohort database, and hence, the health states included in the model can be considered as the most appropriate health states to represent the breast cancer treatment pathways thereby avoiding complicating the model by the inclusion of additional health states that would require further assumptions, and thus, unnecessary uncertainty.

The availability of patient-level data, i.e. longitudinal database, which has recorded the time to one or more events for each patient, allows identifying the most appropriate parametric model, based on the available data, that was used to estimate the hazard rate beyond the follow-up period that consequently has been used to estimate the yearly transition probabilities and LYGs. Moreover, the use of parametric Weibull regression, based on patient-level data, eliminates some of the limitations associated with the Markov model by allowing the transition probabilities to vary with time rather than using constant transition probabilities derived from the literature (173). In addition, Weibull regression was widely adopted in the economic evaluations, reviewed by the NICE technology appraisals, that dealt with metastatic cancer in 2009, which used survival analysis to extrapolate beyond the time horizon (324).

Resource use for each health state were based on actual resource utilised by patients in the cohort database, and thus, reflect the clinical practice in the secondary care. Moreover, different resource use were attached for different years. For patients who

received surgery, costs were incurred within the first year of receiving the treatment only, whilst patients who received adjuvant ETx incurred the costs of ETx for 5 years. Thus, this provides an accurate estimation of costs, without overestimation of the costs.

However, there are some limitations of this study, including lacking of information in primary care setting, resource use and utility values.

One of the limitations arises from using only a secondary database to estimate the cost-effectiveness results. Since the majority of the patients in the cohort study (Chapter 2) were treated and followed in the secondary care, and hence the cohort database did not record the whole care pathway, including primary care. A previously published systematic review of the economic evaluations that compared the clinical and cost-effectiveness of the follow-up cost for primary and secondary cares showed that there was no statistically significant difference in recurrence or survival rate but the follow-up cost in primary care was cheaper than follow-up cost in secondary care (325) and thus, ignoring this type of follow-up may bias the results toward surgery since patients who received surgery have less frequent follow-up as compared to PETx, and therefore limiting the follow-up to the secondary care leads to incur higher cost to the patients in the PETx group. With the increasing incidence of cancer due to an ageing population, moving to cheaper primary follow-up may be recommended. In reality, some breast cancer patients might be followed in the primary care setting, and thus, may incur different costs in terms of follow-up costs, which were not captured in this economic model.

Majorities of the costing studies looked for the hospital settings, even for the studies which looked for primary in addition to secondary care, the contribution of the primary cost to the total costs were very small. Thomas, *et.al*. (2009) (184) and Dolan, *et al*.

(1999) (326) estimated total costs incurred by patients with breast cancer showed that primary care cost (mainly GP visit) contribute to 4.7% and 1.9% of the total care, respectively. In addition, NICE recommended that the patients with breast cancer should be followed in the hospital setting for the initial three years following diagnosis (36).

In addition, despite that the majority of repeated endocrine prescriptions (primary and adjuvant ETx) in the long-term are prescribed in the primary care, and thus, may incur the cost of GP follow-up rather than hospital follow-up costs, current information about whether considering the GP follow-up costs instead of hospital costs for patients who received PETx, or surgery plus adjuvant endocrine would impact on the incremental difference between both treatment strategies were not available from this database.

Finally, there was a lack of other patients' characteristics recorded in the database to predict the transition probabilities, a lack of detailed resource use, and a lack of utility values measured for older women with primary breast cancer at different time periods that may influence the cost-effectiveness results (Section 4.5).

## 4.6. Conclusion

This economic model provides a framework for an iterative economic evaluation, and can be updated when further information is available to inform the cost-effectiveness of using PETx against surgery. The probabilities of PETx were not cost-effective compared to surgery in the overall cohort, whereas patients with H-score over 250 showed a small difference in LYGs in patients who received PETx or surgery, providing a potential for PETx to be cost-effective for this particular group if further research is conducted to eliminate the uncertainty around rejection of PETx. Therefore, further information, including adherence, and resource use that may bias towards surgery is needed to be collected to provide a more robust estimate of the cost-effectiveness of PETx as compared to surgery.

# Chapter 5. Discussion

## 5.1. Summary of the main findings

Overall, this thesis presented an example of an economic evaluation based on an observational study and economic model and addressed the importance of conducting this kind of study in older women with primary breast cancer. The findings of this research summarised the current evidence about the cost-effectiveness of two treatment strategies for the target population that may provide information to inform future clinical decision-making and research in the field.

This research started from a cohort study to explore the effectiveness and cost of different initial treatment strategies for older women with primary breast cancer. Based on a longitudinal database collected at a local hospital in England, the cohort study found that PETx and surgery were the most common initial treatments offered to older women diagnosed with primary breast cancer. Within this cohort, patients who received PETx had a shorter survival time and incurred lower mean costs than those who received PETx, and there is a potential for PETx to be cost-effective. Since there were 519 (77.23%) patients did not observe the long-term outcome (i.e. death) during the longitudinal database follow-up period, and thus, economic modelling was considered to predict the long-term outcomes and costs of the treatment. Given the lack of economic evaluations conducted in older women with primary breast cancer and consequent lack of economic models developed to estimate the lifetime costs and outcomes, therefore, a systematic review of the previously published literature was conducted in younger populations to inform the design of decision analytical modelling in older women with primary breast cancer.

Based on the main findings of the systematic review, a Markov model was designed to assess the cost-effectiveness of PETx and surgery for older women with primary breast cancer in a lifetime horizon combining data from different sources. The results

showed that PETx was not cost-effective as compared to surgery given that the probability of PETx being cost-effective was 24%. However, the subgroup analysis showed small difference in LYGs in both surgical and PETx groups, whilst patients in the PETx group incurred lower costs as compared to the surgical group.

## 5.2. Using observational studies as a source for economic evaluations

Due to the lack of robust evidence-based information on the effectiveness, costs, and treatment pathways of treatment strategies in treating older women with primary breast cancer, an observational study was used as the main source for the economic evaluation. Although the observational study adopted in this research was based on a real-life, longitudinal secondary database and thus enhances the representativeness to the clinical practice, the selection bias and censoring follow-up were the main issue for assessing the clinical and cost-effectiveness of treatment strategies. Some statistical methods such as regression model and extrapolation beyond the follow-up period (Chapter 4.) were used to handle these issues.

This study conducted an economic evaluation based on an observational study which estimated the effectiveness and cost based on real-life data, consequently enhanced the generalisability of the cost-effectiveness results to the clinical practice (172). The LYG and resource utilisation were measured in a routine secondary care setting, which represented the real-life outcomes and costs in a group of patients who actually had been treated in this setting (172,327). The cohort included in the database was representative of the population of older women with primary breast cancer in England with regard to treatment pathways, tumour and patient characteristics (Chapter 2; section **Error! Reference source not found.**).

In terms of clinical practice and treatment pathway, this cohort study may only represent one single setting in England. In addition, the hospital registry did not include

the care pathways incurred in other settings, such as primary care, and hence not able to reflect a complete picture of resource use. However, the nature limitations of observational studies, such as biases and confounding in causal inference are the biggest challenges to derive effectiveness and cost information for economic evaluations.

### 5.2.1. Bias by indication in the observational study

The clinical effectiveness of interventions observed in an observational study is often biased by confounders; for example, the bias by indication (84), which is related to the non-random assignment of treatments given to the patients (84). In real-life practice, patients are not randomised to receive treatments; instead, the physicians' decisions on selecting treatments might be influenced by patients' characteristics and disease condition. As it suggested in the cohort study of older women with primary breast cancer (Chapter 2), in the current practice, PETx was usually offered to patients who were older, with high comorbidities or unfit for surgery. This bias would result in shorter survival times, and consequently, lower costs were incurred in patients received PETx.

The approaches used to derive LYG for the economic modelling can potentially manage the limitation associated with bias by indication and the inexact matching for the age and ER status by generating a survival model adjusted for age, ER positivity and other relevant patient characteristics that allows assuming a similar entry status to the model for both treatment groups (Chapter 4). However, since the estimation of the transition probabilities for this model in this study was also based on the same longitudinal database, which lacks the other patients' characteristics, and thus could bias the estimation of the transition probabilities.

### 5.2.2. Censored follow-up endpoints

Censoring is a common issue in the observational studies, since some patients may not experience the event of interest (i.e. mortality) at the end of follow-up. This is a particularly important issue when the treatment strategies have an impact on survival.

To estimate the cost-effectiveness of PETx against surgery in older women with primary breast cancer, the difference in lifetime costs and outcome between the two treatment strategies needs to be estimated (172,233). However, the natural limitation of the censoring in the longitudinal database inevitably fails to acknowledge the survival time beyond the follow-up period for patients who remain alive in the end of follow-up, which would thus affect the estimation of the LYG. In addition, patients who are living longer would accumulate further resource use in terms of follow-up, medication prescriptions, and treatment for further disease progressions that were not captured on the actual database time horizon (172,233). Therefore, failing to consider the actual survival time (i.e. until a patient's recorded death) due to the censoring issue may mislead the cost-effectiveness result due to incomplete estimate of LYG and associated costs, and hence, extrapolation beyond the observational study period is required to predict the lifetime survival impact and their associated resource use and costs over the patient lifetime horizon.

Economic modelling overcomes the censoring issue by allowing extrapolation of all patients' follow-up times for lifetime horizon (i.e. until they die), and hence, provides a long-term estimate of cost-effectiveness.

### 5.2.3. Quantifying the uncertainty in cost-effectiveness decision making

In addition to the nature limitations of the observational studies in inferencing causality (Section 5.2.1 and 5.2.2), the approach that using a summary estimate of effectiveness and cost in the economic evaluation conducting alongside a clinical trial cannot

represent all the uncertainty for each component used to generate transition probabilities, costs, and utilities. Although distributions were assigned for the total costs and survival time for each treatment strategy in the PSA, uncertainty around each key parameter used to generate these costs and survival time were not considered in the approach.

In contrast, the economic modelling approach (Chapter 4) estimated outcome and cost from a variety of data sources, and distributions were assigned to key parameters used to derive the outcome and cost data. For example, rather than assigning a distribution only for the mean total cost per patient for each treatment, an economic model allows assigning a separate distribution for each unit cost, such as the unit costs of mastectomy or WLE, that were used to estimate the total cost for different health states.

A detailed quantification of the uncertainty around each key parameter is important to assess the costs of the decision uncertainty of PETx adoption in terms of forgone health and resource costs in order to set priorities for further research, i.e. value of information analysis (Chapter 4). In order to estimate the costs of additional research to inform the adoption decision, this would require a full quantification of decision uncertainty (233).

Failure to fully characterise the uncertainty in all key parameters used to estimate the cost-effectiveness ratio would lead to an inaccurate estimation of the expected value of perfect information (328). An economic model allows estimation of the uncertainty around each parameter used to generate the transition probabilities, costs, and utilities. For example, economic model allows assessing the joint uncertainty around the coefficients derived from the Weibull regression and used to generate the transition probabilities for the first and second events, it allows assessing the uncertainty around

each unit cost used to estimate the total cost. However, still the economic model is based on prediction and assumptions that may bias the results, and thus, extensive sensitivity analysis is required to test these assumptions.

## 5.3. Implications of the study findings

### 5.3.1. Therapeutic roles of primary endocrine therapy for older women with primary breast cancer

Surgery and PETx are the main treatments. Although this study was mainly based on a secondary database from a secondary care setting, it still reflects general clinical practices for treating older women with primary breast cancer in the UK, in terms of the commonly used treatments and patients' characteristics. Although there was limited evidence from large RCTs to inform the treatments for older women with primary breast cancer, clinical practitioners commonly use PETx for patients who are unfit for surgery or refuse surgery.

The therapeutic role of PETx in older women with primary breast cancer is still needed to be confirmed. The main findings of this research showed that PETx did not offer any advantage in terms of effectiveness and costs compared with surgery, and thus, there is no strong evidence to recommend replacing surgery by PETx. However, based on the current quality of evidence, the therapeutic role of PETx in older women with primary breast cancer is still inconclusive; in particular, for a special subgroup of patients, more research is needed to explore the effectiveness of PETx.

### 5.3.2. Evidence-based decision-making to sustain geriatric cancer care

Future policy needs to investigate more on geriatric cancer care. As population age increases due to advances in medical technology and improving health care, a greater number of older women is expected to be diagnosed with breast cancer and would

require a surgical treatment. Within the limited budget available to the UK NHS, there may be a scope to consider using cheaper drugs with a lower benefit.

Currently, there is still no evidence-based guidance available for treating older women with primary breast cancer, and thus developing guidance for treating older women with primary breast cancer is necessary. The NICE guideline for treating primary breast cancer, which was mainly based on trials conducted on younger populations, summarised also the evidence from the systematic review of RCTs that were conducted in older women over the age of 70 years (Chapter 1). However, this guideline did not report the role of PETx in older women since there is no previous cost-effectiveness study conducted in older women with primary breast cancer. Based on the main findings of this research, PETx is not more cost-effective as compared to surgery, according to a single observational study, and hence, PETx is not recommended to be the first-line choice for all older women diagnosed with primary breast cancer. However, future research in this area is needed to collect more information, such as frailty and adherence, which may bias the result towards surgery, hence may change the cost-effectiveness of PETx.

Principle of HTA on exisiting less costs and less benefit treatments has not yet developed. Generally, CEA is conducted to assess whether the additional cost of new or established health care technology can be compensated by their additional health benefit as compared to other commonly used alternatives (276). The cost-effectiveness threshold recommended by NICE committee is an estimate of opportunity cost (cost forgone) because other UK NHS activities will not be funded in order to fund the additional costs of new technologies (316). However, there is no clear NICE guidance on whether existing health care technology with less benefit and cost, as the case of this research project, could be of some value to be funded, and thus, guidance to evaluate cheaper treatments is urgently needed.

### 5.3.3. Developing an economic evaluation assessing initial treatment strategies in geriatric breast cancer

The lessons learned from applying the methodologies used in this study may offer some insights to other researchers who would like to conduct similar economic evaluations in the cancer field. Multiple methodologies were used to support the design of an economic evaluation, including epidemiological study, systematic review, economic evaluation based on Markov modelling. To design an economic evaluation in patients with cancer – in general or particularly in breast cancer – the first stage is to identify the outcome measures related to the treatment response in a particular group of patients or with a particular cancer. An observational study based on a pre-existing database may identify the outcomes of interest, and inform the appropriate disease-health states required to be included in the economic model. A systematic review of literature for other economic models conducted in the area is highly recommended. Although this study did not find economic evaluations conducted in the same age-group of interest, it still helped to understand the methodologies used to design the economic models and the sources used to populate these models (Chapter 3).

Furthermore, when using a retrospectively longitudinal database as the main source for conducting an economic model, patients' characteristics that may bias the treatment selection and consequently the final outcomes, hence are important confounders to be managed.

Based on the findings of this study, it is very important to differentiate resource use incurred by patients with primary breast cancer for each health state and their associated costs by different years, since there are some resource use, including surgery and adjuvant therapy, which are not prescribed for a lifetime horizon. In

addition, evaluating long-term utilities should be considered, since utility may improve or get worse following the treatments.

### 5.4. Strengths and limitations of this research

This is the first economic evaluation that compared the use of PETx against surgery in older women with primary breast cancer. It was based on a cohort of older women with primary breast cancer from a single consecutively collected dataset in a hospital in England. The longitudinal clinical parameters collected in this large cohort are representative of general clinical practice in the UK, in terms of patients' characteristics and treatment received. In addition, the decision analytical model was designed based on the results from a systematic review of literature, and thus, the health states which represent the breast cancer treatment pathways are supported by the literature. In addition, Resource use and effectiveness used to estimate the cost-effectiveness ratio were based on the real-life data that would represent the actual resource incurred in clinical practice. Finally, a propensity score was used to overcome the selection bias associated with the non-random assignment.

However, several limitations need to be acknowledged, mainly related to imperfect information. The data was derived from a single database, and thus, the cost estimates were limited to resource use in secondary health care; costs of primary health care were not available for this cohort of patients. A database that incorporates primary and secondary care would be preferable for this type of analysis, although the initial treatment period and early follow-up after a new diagnosis of breast cancer and recurrent breast cancer do mostly occur in secondary care setting (185). Furthermore, several patient characteristics, such as frailty status, adherence, comorbidities, and other unmeasured confounders that may impact on the effectiveness and cost estimates were not recorded, and thus, may bias the results. Finally, since the longitudinal database that was used to estimate the resource use and costs in this

project was not designed to be used later as a vehicle for the economic evaluation, thus some of the variables which were necessary to estimate resource use and costs were not recorded, and thus future research is recommended to collect this information.

## 5.5. Recommendations for future research

### 5.5.1. Primary endocrine therapy for subgroups of older women with primary breast cancer

To define the therapeutic role of PETx and inform a better clinical practice in treating older women with primary breast cancer, future economic evaluations are needed to identify the potential subgroup analysis that may benefit from specific treatment by using a robust estimate of LYG, utility and resources use and considering the impact of frailty, adherence, adverse events and comorbidities on outcomes and costs.

ER status of breast cancer and patients' fitness status are the important factors guided physicians' decision on choosing PETx or surgery for older women with primary breast cancer. Surgery is still considered the first-line treatment, whilst patients who are unfit are not willing to receive surgery, hence other alternatives could be offered, including PETx, primary RTx, or no-treatment (80). Therefore, the investigation of cost-effectiveness comparing PETx against surgery should better be conducted separately in patients with different fitness and ER statuses to ensure an unbiased estimation.

In addition, the cost-effectiveness of PETx against surgery may be different between patients who are adherent or not adherence to ETx, and this question is worth further investigation. Furthermore, using AIs in the adjuvant setting has been proved to be associated with higher disease-free rate in postmenopausal women (97), and with similar progression-free survival as a PETx in older women with primary breast cancer as compared with tamoxifen (66). Therefore, AIs may have a better cost-effectiveness

profile than tamoxifen comparing to surgery as initial treatment in older women with primary breast cancer.

However, information is needed to enable a robust and unbiased judgement on the cost-effectiveness results of these potential further economic evaluations, such as frailty, adherence, adverse events, resource use, and utility data for older women with primary breast cancer.

### 5.5.2. Patients' characteristics that influence on life year gained

#### 5.5.2.1. Measuring frailty in older women with primary breast cancer

Although frailty is an important factor to clinical decision-making in choosing treatments for geriatric patients, it is generally not recorded in RCTs and routine practice. Currently, published RCTs assessing treatment strategies for older women with primary breast cancer were only conducted on patients who were fit for surgery, and most participants in these trials (except for one study) were unselected for ER status (51). Therefore, it is recommended that frailty should be included in future prospective studies assessing the effectiveness of different treatment strategies for older women with primary breast cancer.

Comprehensive geriatric assessment (CGA) score is an index that can be used to distinguish between older patients who are fit to undergo standard cancer treatments and frail older patients who would benefit from modified treatment (329). CGA included domains related to functional status, comorbidity, cognition, mental health status, nutrition, social status and support, fatigue, and assessment for polypharmacy and presence of geriatric syndromes. Various tools and instruments are available for assessing these domains. However, the superiority of one tool over another has not been proven (330). In addition, various classification systems are used to summarise

the scores obtained from the instruments used to assess the geriatric assessment domains (331).

A systematic review, which reviewed the geriatric assessment instruments that have been used for older patients in the cancer setting, showed that the most commonly used summary score was the classification of fit, vulnerable, and frail developed by Balducci and Stanta (2000) (331).

Despite the potential importance of CGA in distinguishing fitness status, it is not used routinely in breast cancer patients worldwide, and thus, implementation of these CGAs in clinical practice (329) should be encouraged in order to estimate the cost-effectiveness of older women with primary breast cancer separated by frailty status.

#### 5.5.2.2. Adherence to primary and adjuvant endocrine therapies

Adherence to ETx (i.e. primary and adjuvant ETx) is very important to consider, since literature demonstrated that non-adherence has an impact on increasing the risk of recurrence events and mortality (332,333), and thus, it consumes resources and associated costs. Adherence to endocrine therapies in clinical practice is relatively lower than in clinical trials, since adherence is closely monitored in clinical trials (334). A retrospective analysis of 2,378 patients with primary breast cancer in the Medicaid program in the USA for the period from 1990 to 1996 showed that adherence to adjuvant tamoxifen was 83%, 68%, 61%, and 50% after 1, 2, 3, and 4 years, respectively, with mean age of (75, SD: 9.5) years (335). AIs were associated with greater adherence compared with tamoxifen; in the Tamoxifen Alone and Combined (ATAC) trial of Arimidex, after 5 years with median follow-up of 68 months, 2.1% and 14.3% of patients who received anastrozole (n=2,618) and tamoxifen (n=2,598), respectively, discontinued their endocrine therapies due to adverse events (77).

Several cohort studies investigated the impact of low adherence to ETx on the breast cancer recurrence and mortality risk. A retrospective cohort of 2,080 patients (mean age: 61, SD: 14 years) with primary breast cancer registered in the Scottish breast cancer registry from 1992 to 2002 (30% over 70 years old), of which 1,633 (79%) received tamoxifen, showed that the risk of overall mortality associated with adjuvant tamoxifen adherence index less than 80% (percentage of the coverage for all the prescriptions for each patient, divided by the duration) was higher compared with tamoxifen adherence index higher than 80% (HR: 1.10; 95%CI: 1.00, 1.21) (332). Moreover, longer-term follow-up (median 4.47 years), including 3,361 patients with primary breast cancer who were registered from 1992 to 2008 in the Scottish breast cancer registry showed that the risk of overall mortality associated with adjuvant tamoxifen or AI adherence less than 80% was higher compared with tamoxifen or AI adherence index higher than 80% (HR: 1.20; 95%CI: 1.03, 1.40; P<0.019) (333).

Measuring adherence for older women would appear to be an important issue, as patients who may adhere to ETx would have higher LYG and lower recurrence and consequently costs, thus this may bias the results towards PETx, and thus, identifying the patients who are adherent to endocrine therapies is needed to provide an unbiased estimate of LYGs and costs. However, since the adherence measure was not recorded in the database, measuring adherence will provide an accurate estimation of LYGs and costs.

#### 5.5.2.3. Other patient characteristics

In addition to ER status and frailty status, some other patient characteristics are also found to be associated with breast cancer survival. Soerjomataram *et al*. (2008) reviewed the prognostic factors that influence the breast cancer survival time and found that patient characteristics – including ethnicity, socioeconomic, comorbidities, tumour size, nodal status and grade, and mutation in the genetic breast cancer

susceptibility gene (BRCA) – have an impact on breast cancer survival (336). These factors can be used as predictors to adjust for the impact of surgery and PETx on the LYG to provide a more robust estimate of the cost-effectiveness results.

### 5.5.3. Adverse events and resource use data

All relevant cost and outcomes associated with these adverse events should be included in the analysis, since treatment strategies, including PETx and surgery, are associated with adverse events that have an impact on patients' treatment outcomes, health-related QoL, and costs. It is important to incorporate the effects of adverse events within the economic models. However, there is a lack of specific guidelines on how to incorporate adverse events in an economic model.

Craig *et al*. (2009) (337) conducted a review to assess the inclusion of adverse events in current HTA. The results showed that 43 (43 of 80; 54%) economic models explicitly included adverse events by incorporating them in a clinical (67%; n=29), cost (79%; n=34) or utility (3%; n=2) parameters (337), such as probability (incidence) of experiencing adverse events, cost of managing adverse events, and utility decrement of experiencing an adverse event, respectively (337).

However, it is difficult to include all adverse events in the three recommended parameters, i.e. incidence, cost and utility, only adverse events, which are most clinically relevant or have the highest impacts on costs and utilities are recommended to be included in an economic model. In addition, guidelines may need to be developed to provide consistent methods to report and incorporate adverse events in economic models.

Collecting detailed data about resource use and associated costs that are necessary for the economic evaluation. In this study, more detailed information is needed for the

variables associated with resource use in the cohort database, including subsequent lines of treatments, type of event associated with each treatment, time to progression on initial and subsequent treatments, the frequency of PETx administration, in order to provide an accurate estimation of the resource use and their associated costs.

### 5.5.4. Utility data for older women with primary breast cancer

Long-term utility data associated with different transition states, including utility following diagnosis, progression-free, and progression is recommended to be directly collected from the population using the EQ-5D questionnaire alongside a prospective trial (i.e. RCTs or prospective observational studies) (338). Population values could be used instead of patients' values since they represent the viewpoint of the tax payer (339), whereas patients may overestimate the utility values, given that they adapt to their disease with time, and hence, they would attach higher utility values to their health states.

## 5.6. Conclusion

PETx was not cost-effectiveness compared to surgery as an initial treatment in older women with primary breast cancer in the economic evaluations based on a longitudinal database of a cohort study collected in a secondary care setting. However, the QALYs in both treatment strategies were slightly similar in the subgroup of patients with H-score over 250. There was a lack of patients' characteristics, including adherence, frailty, adverse events, and comorbidities necessary to estimate a robust estimate of effectiveness and costs, and consequently cost-effectiveness results.

Based on the current available evidence, it is not recommended to replace surgery by PETx as the first-line treatment. However, there is still a need to develop clinical guidance for managing older women with primary breast cancer, and to explore cheaper treatment options for this fast growing geriatric cancer.

Future research is recommended to collect further information on patients' characteristics that influence LYG, including frailty and adherence, detailed resource use, including resource use related to manage adverse events that impact on the cost estimation. In particular, studies on gathering utility data for older women will provide a fair judgment on comparing the cost-effectiveness between PETx and surgery. Finally, conducting a further economic evaluation in appropriate subgroups of older women with primary breast cancer will also identify the patient groups that could benefit the most from PETx.

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## Appendices

### Appendix 1. Variables recorded in the database and their definitions

| Variables | Definition |
|---|---|
| **Patients Characteristics** | |
| Age (years) | Age at time of presentation |
| Follow-up (months) | Time from date of diagnosis until death during the follow-up period, lost to follow-up or end of follow-up period |
| **Tumour characteristics** | |
| **All patients based on NCB)** | |
| Clinical size of tumour (cm) | Size of tumour on NCB |
| Histological grade | Classified as grades 1 to 3 according Scarf-Bloom-Richardson criteria |
| Histological type | e.g. DCIS, invasive, tubulo-mix |
| ER status since 1990 | ER considered positive when the H-score ≥50 or positive on charcoal coated method |
| **Surgical specimens (for surgery treatment only)** | |
| Histological grade | Classified as grades 1 to 3 according to Scarf-Bloom-Richardson criteria |
| Histological type | e.g. DCIS, invasive, tubulo-mix |
| Pathological size (cm) | Size of tumour on surgical specimen |
| Stage | Stage 1 = 0 lymph node, stage 2 = 1-3 lymph nodes, and stage 3 = more than 4 lymph nodes |
| ER status since 1990 | ER considered positive when the H-score ≥50 or positive on charcoal coated method |
| **Treatment** | |
| Initial treatment | The first treatment received by patients once they are diagnosed with breast cancer, such as surgery, PETx, primary RTx |
| Adjuvant treatment | Treatments that are used after surgery, such as tamoxifen, RTx, CTx, anastrazole |
| Second, third, fourth,fifth, and sixth line treatments for PETx | Subsequent line of treatment received by the patients either due to progression or treatment adverse events: surgery, PETx, primary RTx |

**(Continue Appendix 1.)**

| Variables | Definition |
|---|---|
| **Treatment outcomes** | |
| **All patients** | |
| Metastases | Appearance of tumour at distant organ, e.g. liver, bone, contralateral axillary lymph node |
| Contralateral tumour | Appearance of new primary tumour at the opposite side of the breast |
| Death | Death due to breast cancer , non-breast cancer cause, or other causes |
| **Surgery** | |
| Local recurrence | Appearance of tumour in the same breast after the surgical procedure |
| Regional recurrence | Appearance of tumour in ipsilateral axillary lymph node |
| **Non-surgical treatment** | |
| Response at 6 months (for initial and subsequent line treatment) | Complete disappearance of the tumour lesion CR; more than 50% reduction of the lesion PR, less than 25% increase or less than 50% reduction of the tumour lesion SD, or more than 25% increase of tumour or appearance of new tumour lesion PD |
| Best response (for initial treatment only) | Best response achieved before progression, i.e. whether CR, SD, PR, or PD |
| Progression status (for initial and subsequent treatment) | PD, non-progression, or therapy change |
| **Time to events** | |
| **All patients** | |
| Time to metastases | Time from date of diagnosis until the appearance of tumour in distant organ |
| Time to contralateral tumour | Time from date of diagnosis until the appearance of contralateral tumour |
| Overall survival time | Time from date of diagnosis until death due to any cause, loss to follow-up or end of follow-up duration (for patients who were discharged back to the GP, the date of death was supplemented by information from their GP) |
| **Surgery** | |
| Time to local recurrence | Time from date of diagnosis until the appearance of local recurrence |
| Time to regional recurrence | Time from date of diagnosis until the appearance of regional recurrence |
| **Non-surgical treatment** | |
| Time to progression (for initial and subsequent line treatment) | Time from date of diagnosis until progression or therapy change |

**(Note)** WLE: wide local excision; NCB: needle core biopsy; ER: oestrogen receptor; PETx: primary endocrine therapy; DCIS: ductal carcinoma in situ; RTx: radiotherapy, CTx: chemotherapy, PD: progressive disease, CR: complete response, PR: partial response, PD: progressive disease.

**Appendix 2. Categories of health care resources and method of their identification**

| Resource utilisation | Patient events | Episode | Method of identification | Assumptions |
|---|---|---|---|---|
| **Secondary care** | | | | |
| **Inpatient setting** | | | | |
| Surgical procedures | Initial treatment or subsequent-lines of treatment | **Frequency**<br>Patients who had one surgery during the study follow-up period were considered to have one spell with one episode, whilst patients who had multiple surgical admission were considered to have multiple spells with one episode per spell | **Frequency**<br>Recorded 'type of treatment' in the cohort database | None |
| **Outpatient setting** | | | | |
| Endocrine therapy | Initial treatment or subsequent-lines of treatment | **Dose and frequency**<br>Recommended dosage regimen (see Table 2.2).<br><br>**Duration**<br>Lifetime duration if the patients did not progress.<br>'Time to progression' if the patients progressed or changed therapy. | **Frequency**<br>BNF<br>**Dose**<br>BNF<br>**Duration**<br>Recorded 'survival time' in the cohort database for patients who did not progress.<br>Recorded 'time to progression' variable in the database for patients who progressed. | Patients were considered to finish the whole endocrine therapy pack. |

**(Continue Appendix 2.)**

| Resource utilisation | Patients events | Episode | Method of identification | Assumptions |
|---|---|---|---|---|
| **Outpatient setting** | | | | |
| | Adjuvant treatment | **Dose and Frequency**<br>Recommended dosage regimen (see Table 2.2).<br><br>**Duration**<br>Five-year duration if the patients did not progress for five years on surgical treatment.<br>'Time to recurrence' on surgical treatment if the patients 'disease progressed. | **Frequency**<br>BNF<br>**Dose**<br>BNF<br>**Duration**<br>Clinical practice for patients who did not progress.<br>The 'time to recurrence' variable recorded in the database for patients who progressed. | |
| Radiotherapy | Initial line of treatment | **Dose and frequency**<br>35 fractions of external beam radiation once daily, 5 days per week.<br>**Duration**<br>7 weeks | **Type of radiotherapy**<br>Clinical practice<br>**Frequency**<br>Clinical practice<br>**Duration**<br>Clinical practice | |
| | Subsequent lines of treatment<br>Adjuvant treatment | **Dose and frequency**<br>25 fractions of external beam radiation once daily, 5 days per week for patients treated before 2008;<br>15 fractions of hypofractionated external beam radiotherapy 5 days per week for patients treated after 2008<br>**Duration**<br>Five weeks for external beam radiation<br>Three weeks for hypofractionated external beam radiotherapy | **Type of radiotherapy**<br>Clinical practice<br>**Frequency**<br>Clinical practice<br>**Duration**<br>Clinical practice | The exact year of the introduction of the hypofractionated radiotherapy was based on the START trial. |

**(Continue Appendix 2.)**

| Resource utilisation | Patients events | Episode | Method of identification | Assumptions |
|---|---|---|---|---|
| **Outpatient setting** | | | | |
| | Planning of radiotherapy | **Frequency**<br>One planning meeting before the commencement of RTx treatment | **Frequency**<br>Clinical practice | |
| Chemotherapy | Adjuvant treatment | **Dose, frequency, and duration**<br>FEC 75 mg for six cycles for patients with negative lymph node, FEC 100 mg for three cycles followed by docetaxel for other three cycles for patients with positive lymph node | **Type of CTx**<br>Clinical practice<br>**Dose, Frequency**<br>Clinical practice<br>**Duration**<br>Clinical practice | None |
| | Administration of CTx | **Dose, frequency, and duration**<br>One administration per cycle | **Dose, frequency, and duration**<br>Clinical practice | |
| Outpatient visits | New attendance | **Frequency**<br>One visit after disease progression | **Frequency**<br>Recorded 'progression status' variable in the database for patients on non-surgical treatment<br>Recorded 'recurrence status' variable in the database for patients on surgical treatment | None |
| | Diagnostic images: CT scan for pelvis, abdomen, and chest | **Frequency**<br>One CT scan after disease progression | **Frequency**<br>Recorded 'progression status' variable in the database for patients on non-surgical treatment<br>Recorded 'recurrence status' variable in the database for patients on surgical treatment | |

**(Continue Appendix 2.)**

| Resource utilisation | Patients events | Episode | Method of identification | Assumptions |
|---|---|---|---|---|
| | Follow-up | **Frequency**<br>Yearly follow-up for patients on surgical treatment<br>At 6 weeks, 3 months and 6 months, and then every 6 months for patients on non-surgical treatment<br><br>**Duration**<br>Lifetime | **Frequency**<br>For patients who were on first-line treatment and their disease did not progress. The recorded time to death or time to last follow-up duration divided by 12 months in case of surgery, or 6 months in case of non-surgical treatment<br>For patients who were progressed, the frequency was identified from the recorded 'time to progression' or 'time to recurrence' variable in the database divided by 12 or 6 months based on the type of treatment.<br>For patients who were on a subsequent line of treatment and their disease did not progress, the frequency of follow-up was Identified from the recorded time from last progression or recurrence until the time to death or time to last breast cancer follow-up divided by 12 or 6 months based on the type of treatment. | None |
| | Multidisciplinary team meeting (MDT) | **Frequency**<br>One meeting after any surgical procedure to discuss the results of core or needle core biopsy | **Frequency**<br>Any record of the surgical treatment in the database ,whether it is initial or subsequent line of treatment | None |

Note: GP: general practitioner; ETx: endocrine therapy; PETx: primary endocrine therapy; RTx: radiotherapy; FEC: fluorouracil (5FU), epirubicin, and cyclophosphamide; NA: not applicable; NICE: National Institute for Health and Care Excellence; START: Standardisation of Breast Radiotherapy trial; CT scan: computerised tomography scan.

## Appendix 3. OPCS codes for surgical procedures

| OPCS codes | Description |
|---|---|
| B274 | Total mastectomy |
| B282 | Partial excision of breast |
| B285 | Wire-guided partial excision of breast |
| T852 | Axillary dissection |
| T873 | SLNB |

**(Note)** OPCS**:** operating procedure code supplements; SLNB: sentinel lymph node dissection

## Appendix 4. HRG codes generated from the HRG grouper for the surgical procedures

| HRG codes | Surgical procedures |
|---|---|
| JA38C | Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 0-1 |
| JA20F | Unilateral Major Breast Procedures with CC Score 0-2 |
| SA17H | Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2 |

**(Note)** CC: Charlson Comorbidity; HRG: Healthcare Resource Groups

## Appendix 5. HRG codes derived from NHS reference costs for chemotherapy, radiotherapy, outpatient visits, and diagnostic images

| HRG codes | Description |
|---|---|
| SB02Z | Procure chemotherapy drugs for regimens in FEC 75 or FCE 100 |
| SB06Z | Procure chemotherapy drugs for regimens in Docetaxel 75 |
| SB12Z | Deliver simple Parenteral Chemotherapy at first attendance |
| SC23Z | Deliver a fraction of complex treatment on a megavoltage machine |
| SC51Z | Preparation for complex conformal radiotherapy |
| WF01A | Non-admitted face to face attendance, breast surgery follow-up |
| WF01B | Non-admitted face to face attendance, first |
| CMDT_B | Breast cancer MDT meetings |
| RA13Z | Computerised Tomography Scan, three areas with contrast |

**(Note)** FEC: fluorouracil (5FU), epirubicin, and cyclophosphamide; MDT :multidisciplinary team; HRG: Healthcare Resource Groups.

## Appendix 6. Search strategies in different databases

### Search strategies in Medline in process (1946)

| | | |
|---|---|---|
| 1 | economics/ | 0 |
| 2 | exp "costs and cost analysis"/ | 0 |
| 3 | economics, dental/ | 0 |
| 4 | exp "economics, hospital"/ | 0 |
| 5 | economics, medical/ | 0 |
| 6 | economics, nursing/ | 0 |
| 7 | economics, pharmaceutical/ | 0 |
| 8 | (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 45554 |
| 9 | (expenditure$ not energy).ti,ab. | 1337 |
| 10 | value for money.ti,ab. | 95 |
| 11 | budget$.ti,ab. | 2040 |
| 12 | or/1-11 | 47618 |
| 13 | ((energy or oxygen) adj cost).ti,ab. | 246 |
| 14 | (metabolic adj cost).ti,ab. | 92 |
| 15 | ((energy or oxygen) adj expenditure).ti,ab. | 1094 |
| 16 | or/13-15 | 1382 |
| 17 | 12 not 16 | 47213 |
| 18 | letter.pt. | 26492 |
| 19 | editorial.pt. | 15629 |
| 20 | historical article.pt. | 3 |
| 21 | or/18-20 | 42124 |
| 22 | 17 not 21 | 46735 |
| 23 | Animals/ | 27 |
| 24 | Humans/ | 84 |
| 25 | 23 not (23 and 24) | 5 |
| 26 | 22 not 25 | 46735 |
| 27 | Breast Neoplasms/dt, ec, mo, rt, su, th [Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 0 |
| 28 | Carcinoma, Ductal, Breast/dt, ec, mo, rt, su, th [Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 0 |
| 29 | ((early or primary or operable or early stage or stage I or stage II) adj (breast adj (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumo?r))).ti,ab. | 771 |
| 30 | 27 or 28 or 29 | 771 |
| 31 | *Breast Neoplasms/an, ah, bl, bs, cf, ci, ch, cl, co, cn, di, dh, em, en, ep, eh, et, ge, hi, im, lj, me, mi, nu, ps, pa, ph, pp, pc, px, ra, ri, rh, sc, se, tm, us, ul, ur, ve, vi [Analysis, Anatomy & Histology, Blood, Blood Supply, Cerebrospinal Fluid, Chemically Induced, Chemistry, Classification, Complications, Congenital, Diagnosis, Diet Therapy, Embryology, Enzymology, Epidemiology, Ethnology, Etiology, Genetics, History, Immunology, Legislation & Jurisprudence, Metabolism, Microbiology, Nursing, Parasitology, Pathology, Physiology, Physiopathology, Prevention & Control, Psychology, | 3 |

| | | |
|---|---|---|
| | Radiography, Radionuclide Imaging, Rehabilitation, Secondary, Secretion, Transmission, Ultrasonography, Ultrastructure, Urine, Veterinary, Virology] | |
| 32 | *Carcinoma, Ductal, Breast/bl, bs, cf, ci, ch, cl, co, di, dh, en, ep, eh, et, ge, hi, im, me, mi, nu, ps, pa, pp, pc, px, ra, ri, rh, sc, se, us, ul, ur, ve, vi [Blood, Blood Supply, Cerebrospinal Fluid, Chemically Induced, Chemistry, Classification, Complications, Diagnosis, Diet Therapy, Enzymology, Epidemiology, Ethnology, Etiology, Genetics, History, Immunology, Metabolism, Microbiology, Nursing, Parasitology, Pathology, Physiopathology, Prevention & Control, Psychology, Radiography, Radionuclide Imaging, Rehabilitation, Secondary, Secretion, Ultrasonography, Ultrastructure, Urine, Veterinary, Virology] | 0 |
| 33 | Breast Neoplasms/ge [Genetics] | 1 |
| 34 | *Neoplasms/ge [Genetics] | 0 |
| 35 | exp gene expression/ or exp gene expression regulation/ or exp gene rearrangement/ or exp genetic structures/ or exp genetic variation/ | 9 |
| 36 | exp Genetic Testing/ | 0 |
| 37 | exp Gene Expression Profiling/ | 0 |
| 38 | Tumor Markers, Biological/ | 2 |
| 39 | *Tumor Markers, Biological/ | 2 |
| 40 | *Granulocyte Colony-Stimulating Factor/ | 0 |
| 41 | *Chemotherapy-Induced Febrile Neutropenia/ | 0 |
| 42 | *Surgical Wound Infection/ | 0 |
| 43 | *Bone Neoplasms/ | 1 |
| 44 | *Anemia/ | 0 |
| 45 | exp *Carcinoma, Intraductal, Noninfiltrating/ | 0 |
| 46 | 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 | 12 |
| 47 | 30 not 46 | 771 |
| 48 | exp Mastectomy, Extended Radical/ or exp Mastectomy, Segmental/ or Mastectomy/ or exp Mastectomy, Radical/ or exp Mastectomy, Modified Radical/ or exp Mastectomy, Simple/ | 0 |
| 49 | (mastectom* or operat* or surg* or (breast adj conserv*) or lumpectom* or "wide local excision" or segmentectom* or mammectom* or quadrantectom*).ti,ab. | 138282 |
| 50 | Brachytherapy/ae, ec, mo [Adverse Effects, Economics, Mortality] | 0 |
| 51 | Radiotherapy/ae, co, ec, mo, su [Adverse Effects, Complications, Economics, Mortality, Surgery] | 0 |
| 52 | Radiotherapy, Adjuvant/ae, ec, mo [Adverse Effects, Economics, Mortality] | 0 |
| 53 | (radiotherap* or brachytherap*).ti,ab. | 7349 |
| 54 | Antineoplastic Agents, Hormonal/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 55 | Tamoxifen/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 56 | Aromatase Inhibitors/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |

| | | |
|---|---|---|
| 57 | (tamoxifen or anastrozole or letrozole or exemestane or (aromatase adj inhibitor*) or ((endocrine or hormon*) adj therap*)).ti,ab. | 2145 |
| 58 | Drug Therapy/co, ec, mo, su [Complications, Economics, Mortality, Surgery] | 0 |
| 59 | Chemotherapy, Adjuvant/ae, ec, mo [Adverse Effects, Economics, Mortality] | 0 |
| 60 | Taxoids/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 61 | Antimetabolites, Antineoplastic/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 62 | Cyclophosphamide/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 63 | Doxorubicin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 64 | Epirubicin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 65 | Methotrexate/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 66 | Mitomycin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 67 | Fluorouracil/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 68 | (chemotherap* or cyclophosphamide or methotrexate or fluorouracil or doxorubicin or adriamycin or epirubicin or mitozantrone or mitomycin or paclitaxel or docetaxel).ti,ab. | 21742 |
| 69 | (trastuzumab or lapatinib).ti,ab. | 629 |
| 70 | Antibodies, Monoclonal, Humanized/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 0 |
| 71 | 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 | 160163 |
| 72 | Disease-Free Survival/ or Survival Analysis/ or Survival/ or Survival Rate/ | 1 |
| 73 | Recurrence/dt, ec, su, th [Drug Therapy, Economics, Surgery, Therapy] | 0 |
| 74 | Neoplasm Recurrence, Local/co, dt, ec, mo, rt, su, th [Complications, Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 0 |
| 75 | (recurrence* or relapse*).ti,ab. | 19651 |
| 76 | quality-adjusted life years/ | 0 |
| 77 | "Quality of Life"/ | 0 |
| 78 | Treatment Outcome/ | 7 |
| 79 | (quality adj life).ti,ab. | 18 |
| 80 | adverse event$.ti,ab. | 7301 |
| 81 | 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 | 26540 |
| 82 | 26 and 47 and 71 and 81 | 10 |

## Search strategies in Medline 1964

| | | |
|---|---|---|
| 1 | economics/ | 26511 |
| 2 | exp "costs and cost analysis"/ | 178391 |
| 3 | economics, dental/ | 1853 |
| 4 | exp "economics, hospital"/ | 19252 |
| 5 | economics, medical/ | 8583 |
| 6 | economics, nursing/ | 3889 |
| 7 | economics, pharmaceutical/ | 2508 |
| 8 | (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. | 410497 |
| 9 | (expenditure$ not energy).ti,ab. | 16836 |
| 10 | value for money.ti,ab. | 856 |
| 11 | budget$.ti,ab. | 16771 |
| 12 | or/1-11 | 533335 |
| 13 | ((energy or oxygen) adj cost).ti,ab. | 2606 |
| 14 | (metabolic adj cost).ti,ab. | 730 |
| 15 | ((energy or oxygen) adj expenditure).ti,ab. | 15615 |
| 16 | or/13-15 | 18271 |
| 17 | 12 not 16 | 529265 |
| 18 | letter.pt. | 804082 |
| 19 | editorial.pt. | 333780 |
| 20 | historical article.pt. | 298888 |
| 21 | or/18-20 | 1422172 |
| 22 | 17 not 21 | 501453 |
| 23 | Animals/ | 5248552 |
| 24 | Humans/ | 13273846 |
| 25 | 23 not (23 and 24) | 3812070 |
| 26 | 22 not 25 | 470043 |
| 27 | Breast Neoplasms/dt, ec, mo, rt, su, th [Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 90467 |
| 28 | Carcinoma, Ductal, Breast/dt, ec, mo, rt, su, th [Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 5038 |
| 29 | ((early or primary or operable or early stage or stage I or stage II) adj (breast adj (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumo?r))).ti,ab. | 12916 |
| 30 | 27 or 28 or 29 | 95638 |
| 31 | *Breast Neoplasms/an, ah, bl, bs, cf, ci, ch, cl, co, cn, di, dh, em, en, ep, eh, et, ge, hi, im, lj, me, mi, nu, ps, pa, ph, pp, pc, px, ra, ri, rh, sc, se, tm, us, ul, ur, ve, vi [Analysis, Anatomy & Histology, Blood, Blood Supply, Cerebrospinal Fluid, Chemically Induced, Chemistry, Classification, Complications, Congenital, Diagnosis, Diet Therapy, Embryology, Enzymology, Epidemiology, Ethnology, Etiology, Genetics, History, Immunology, Legislation & Jurisprudence, Metabolism, Microbiology, Nursing, Parasitology, Pathology, Physiology, Physiopathology, Prevention & Control, Psychology, Radiography, Radionuclide Imaging, Rehabilitation, Secondary, | 120230 |

| | | |
|---|---|---|
| | Secretion, Transmission, Ultrasonography, Ultrastructure, Urine, Veterinary, Virology] | |
| 32 | *Carcinoma, Ductal, Breast/bl, bs, cf, ci, ch, cl, co, di, dh, en, ep, eh, et, ge, hi, im, me, mi, nu, ps, pa, pp, pc, px, ra, ri, rh, sc, se, us, ul, ur, ve, vi [Blood, Blood Supply, Cerebrospinal Fluid, Chemically Induced, Chemistry, Classification, Complications, Diagnosis, Diet Therapy, Enzymology, Epidemiology, Ethnology, Etiology, Genetics, History, Immunology, Metabolism, Microbiology, Nursing, Parasitology, Pathology, Physiopathology, Prevention & Control, Psychology, Radiography, Radionuclide Imaging, Rehabilitation, Secondary, Secretion, Ultrasonography, Ultrastructure, Urine, Veterinary, Virology] | 6661 |
| 33 | Breast Neoplasms/ge [Genetics] | 31138 |
| 34 | *Neoplasms/ge [Genetics] | 13419 |
| 35 | exp gene expression/ or exp gene expression regulation/ or exp gene rearrangement/ or exp genetic structures/ or exp genetic variation/ | 2167849 |
| 36 | exp Genetic Testing/ | 25843 |
| 37 | exp Gene Expression Profiling/ | 78837 |
| 38 | Tumor Markers, Biological/ | 83063 |
| 39 | *Tumor Markers, Biological/ | 45132 |
| 40 | *Granulocyte Colony-Stimulating Factor/ | 7412 |
| 41 | *Chemotherapy-Induced Febrile Neutropenia/ | 9 |
| 42 | *Surgical Wound Infection/ | 16386 |
| 43 | *Bone Neoplasms/ | 36592 |
| 44 | *Anemia/ | 20154 |
| 45 | exp *Carcinoma, Intraductal, Noninfiltrating/ | 5276 |
| 46 | 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 | 2427909 |
| 47 | 30 not 46 | 52617 |
| 48 | exp Mastectomy, Extended Radical/ or exp Mastectomy, Segmental/ or Mastectomy/ or exp Mastectomy, Radical/ or exp Mastectomy, Modified Radical/ or exp Mastectomy, Simple/ | 22613 |
| 49 | (mastectom* or operat* or surg* or (breast adj conserv*) or lumpectom* or "wide local excision" or segmentectom* or mammectom* or quadrantectom*).ti,ab. | 1661909 |
| 50 | Brachytherapy/ae, ec, mo [Adverse Effects, Economics, Mortality] | 2869 |
| 51 | Radiotherapy/ae, co, ec, mo, su [Adverse Effects, Complications, Economics, Mortality, Surgery] | 16464 |
| 52 | Radiotherapy, Adjuvant/ae, ec, mo [Adverse Effects, Economics, Mortality] | 1704 |
| 53 | (radiotherap* or brachytherap*).ti,ab. | 114384 |
| 54 | Antineoplastic Agents, Hormonal/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 10656 |
| 55 | Tamoxifen/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 10037 |
| 56 | Aromatase Inhibitors/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 2132 |
| 57 | (tamoxifen or anastrozole or letrozole or exemestane or (aromatase adj inhibitor*) or ((endocrine or hormon*) adj therap*)).ti,ab. | 37856 |

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|---|---|---|
| 58 | Drug Therapy/co, ec, mo, su [Complications, Economics, Mortality, Surgery] | 1303 |
| 59 | Chemotherapy, Adjuvant/ae, ec, mo [Adverse Effects, Economics, Mortality] | 1357 |
| 60 | Taxoids/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 5667 |
| 61 | Antimetabolites, Antineoplastic/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 11821 |
| 62 | Cyclophosphamide/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 35348 |
| 63 | Doxorubicin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 28340 |
| 64 | Epirubicin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 3656 |
| 65 | Methotrexate/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 25293 |
| 66 | Mitomycin/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 5255 |
| 67 | Fluorouracil/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 27329 |
| 68 | (chemotherap* or cyclophosphamide or methotrexate or fluorouracil or doxorubicin or adriamycin or epirubicin or mitozantrone or mitomycin or paclitaxel or docetaxel).ti,ab. | 343215 |
| 69 | (trastuzumab or lapatinib).ti,ab. | 4712 |
| 70 | Antibodies, Monoclonal, Humanized/ad, ae, ec, tu, to [Administration & Dosage, Adverse Effects, Economics, Therapeutic Use, Toxicity] | 6455 |
| 71 | 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 | 2068080 |
| 72 | Disease-Free Survival/ or Survival Analysis/ or Survival/ or Survival Rate/ | 246164 |
| 73 | Recurrence/dt, ec, su, th [Drug Therapy, Economics, Surgery, Therapy] | 12 |
| 74 | Neoplasm Recurrence, Local/co, dt, ec, mo, rt, su, th [Complications, Drug Therapy, Economics, Mortality, Radiotherapy, Surgery, Therapy] | 25755 |
| 75 | (recurrence* or relapse*).ti,ab. | 272809 |
| 76 | quality-adjusted life years/ | 6774 |
| 77 | "Quality of Life"/ | 114259 |
| 78 | Treatment Outcome/ | 611020 |
| 79 | (quality adj life).ti,ab. | 205 |
| 80 | adverse event$.ti,ab. | 68715 |
| 81 | 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 | 1124110 |
| 82 | 26 and 47 and 71 and 81 | 524 |
| 83 | limit 82 to (english language and humans) | 484 |
| 84 | Letter/ | 804082 |
| 85 | Editorial/ | 333780 |
| 86 | 84 or 85 | 1137797 |
| 87 | 83 not 86 | 484 |

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|---|---|---|
| 88 | "Review"/ | 1846798 |
| 89 | 87 not 88 | 366 |

**Search strategies in EMBASE 1974**

| | | |
|---|---|---|
| 1 | Socioeconomics/ | 107880 |
| 2 | Cost benefit analysis/ | 63714 |
| 3 | Cost effectiveness analysis/ | 95868 |
| 4 | Cost of illness/ | 13894 |
| 5 | Cost control/ | 47647 |
| 6 | Economic aspect/ | 102653 |
| 7 | Financial management/ | 99721 |
| 8 | Health care cost/ | 126691 |
| 9 | Health care financing/ | 11357 |
| 10 | Health economics/ | 33345 |
| 11 | Hospital cost/ | 13522 |
| 12 | (fiscal or financial or finance or funding).tw. | 102734 |
| 13 | Cost minimization analysis/ | 2426 |
| 14 | (cost adj estimate$).mp. | 1949 |
| 15 | (cost adj variable$).mp. | 154 |
| 16 | (unit adj cost$).mp. | 2381 |
| 17 | or/1-16 | 654963 |
| 18 | *breast cancer/dm, dt, su, th, rt, si [Disease Management, Drug Therapy, Surgery, Therapy, Radiotherapy, Side Effect] | 48957 |
| 19 | *breast tumor/dm, dt, rt, si, su, th [Disease Management, Drug Therapy, Radiotherapy, Side Effect, Surgery, Therapy] | 19900 |
| 20 | *breast adenocarcinoma/dm, dt, rt, si, su, th [Disease Management, Drug Therapy, Radiotherapy, Side Effect, Surgery, Therapy] | 467 |
| 21 | *breast carcinoma/dm, dt, rt, si, su, th [Disease Management, Drug Therapy, Radiotherapy, Side Effect, Surgery, Therapy] | 9061 |
| 22 | *estrogen receptor positive breast cancer/dm, dt, rt, si, su, th [Disease Management, Drug Therapy, Radiotherapy, Side Effect, Surgery, Therapy] | 194 |
| 23 | ((early or primary or operable or early stage or stage I or stage II) adj (breast adj (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumo?r))).ti,ab. | 18401 |
| 24 | 18 or 19 or 20 or 21 or 22 or 23 | 89014 |
| 25 | *breast cancer/co, cn, di, dr, ep, et, pc, rh [Complication, Congenital Disorder, Diagnosis, Drug Resistance, Epidemiology, Etiology, Prevention, Rehabilitation] | 42281 |
| 26 | *breast tumor/co, cn, di, an, dr, ep, et, pc, rh [Complication, Congenital Disorder, Diagnosis, Drug Analysis, Drug Resistance, Epidemiology, Etiology, Prevention, Rehabilitation] | 18832 |
| 27 | *breast carcinoma/co, cn, di, dr, ep, et, pc, rh [Complication, Congenital Disorder, Diagnosis, Drug Resistance, Epidemiology, Etiology, Prevention, Rehabilitation] | 9352 |
| 28 | *breast adenocarcinoma/co, cn, di, dr, ep, et, pc, rh [Complication, Congenital Disorder, Diagnosis, Drug Resistance, Epidemiology, Etiology, Prevention, Rehabilitation] | 395 |
| 29 | *estrogen receptor positive breast cancer/di, dr, ep, et, pc [Diagnosis, Drug Resistance, Epidemiology, Etiology, Prevention] | 73 |

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|---|---|---|
| 30 | exp gene expression/ or exp gene expression assay/ | 921274 |
| 31 | exp gene expression profiling/ | 55977 |
| 32 | exp gene/ | 633624 |
| 33 | exp *genomics/ | 18001 |
| 34 | exp genetic analysis/ | 239397 |
| 35 | exp gene amplification/ | 544896 |
| 36 | exp pharmacogenetics/ | 20900 |
| 37 | exp *tumor biopsy/ | 830 |
| 38 | exp *biological marker/ or exp *molecular marker/ or exp *tumor marker/ | 88660 |
| 39 | exp *febrile neutropenia/ | 1868 |
| 40 | exp granulocyte colony stimulating factor/ | 31125 |
| 41 | exp *anemia/ | 127859 |
| 42 | exp *bone metastasis/ | 11235 |
| 43 | exp *intraductal carcinoma/ | 3068 |
| 44 | *heart metastasis/ or *kidney metastasis/ or *spine metastasis/ or *visceral metastasis/ or *colon metastasis/ or *pleura metastasis/ or *bone marrow metastasis/ or *melanoma metastasis/ or *bladder metastasis/ or *metastasis/ or *adrenal metastasis/ or *skin metastasis/ or *ovary metastasis/ or *spleen metastasis/ or *central nervous system metastasis/ or *port site metastasis/ or *muscle metastasis/ or *bone metastasis/ or *neck metastasis/ or *distant metastasis/ or *liver metastasis/ or *orbit metastasis/ or *lung metastasis/ or *colorectal liver metastasis/ or *meningeal metastasis/ or *brain metastasis/ or *esophagus metastasis/ or *mediastinum metastasis/ or *thyroid metastasis/ or *pancreas metastasis/ or *soft tissue metastasis/ or *spinal cord metastasis/ or *breast metastasis/ | 110695 |
| 45 | exp *abdominal tumor/ | 18752 |
| 46 | exp *abdominal tumor/ or exp *cardiovascular system tumor/ or exp *digestive system tumor/ or exp *endocrine tumor/ or exp *"head and neck tumor"/ or exp *hematopoietic system tumor/ or exp *locomotor system tumor/ or exp *lymphatic system tumor/ or exp *"neoplasms of the thorax and thoracic cavity"/ or exp *nervous system tumor/ or exp *pelvis tumor/ or exp *respiratory tract tumor/ or exp *reticuloendothelial neoplasm/ or exp *skin tumor/ or exp *soft tissue tumor/ or exp *urogenital tract tumor/ | 1885885 |
| 47 | 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 | 3764635 |
| 48 | 24 not 47 | 46355 |
| 49 | exp partial mastectomy/ or mastectomy/ or exp segmental mastectomy/ | 36246 |
| 50 | (mastectom* or operat* or surg* or (breast adj conserv*) or lumpectom* or "wide local excision" or segmentectom* or mammectom* or quadrantectom*).ti,ab. | 2267672 |
| 51 | cancer chemotherapy/ | 161182 |
| 52 | adjuvant chemotherapy/ | 23180 |
| 53 | chemotherapy/ | 77466 |
| 54 | combination chemotherapy/ | 31360 |
| 55 | cancer combination chemotherapy/ | 63793 |

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|---|---|---|
| 56 | taxoid/ae, cb, ct, dt, to, pe [Adverse Drug Reaction, Drug Combination, Clinical Trial, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 637 |
| 57 | antineoplastic antimetabolite/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 1804 |
| 58 | cyclophosphamide/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 111457 |
| 59 | methotrexate/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 84989 |
| 60 | fluorouracil/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 66857 |
| 61 | doxorubicin/ae, ct, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 77681 |
| 62 | doxorubicin/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 81367 |
| 63 | doxorubicin/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 81367 |
| 64 | epirubicin/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 17651 |
| 65 | paclitaxel/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 41308 |
| 66 | docetaxel/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 24823 |
| 67 | mitomycin/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 6572 |
| 68 | mitoxantrone/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 13772 |
| 69 | (chemotherap* or cyclophosphamide or methotrexate or fluorouracil or doxorubicin or adriamycin or epirubicin or mitozantrone or mitomycin or paclitaxel or docetaxel).ti,ab. | 497593 |
| 70 | (endocrine or (hormon* adj therap*) or tamoxifen or anastrozole or letrozole or exemestane or (aromatase adj inhibitor*)).ti,ab. | 164168 |
| 71 | hormonal therapy/ | 26059 |
| 72 | cancer hormone therapy/ | 12988 |
| 73 | trastuzumab/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 13971 |
| 74 | monoclonal antibody/ae, ct, cb, dt, to, pe [Adverse Drug Reaction, Clinical Trial, Drug Combination, Drug Therapy, Drug Toxicity, Pharmacoeconomics] | 23856 |
| 75 | (trastuzumab or lapatinib).ti,ab. | 9336 |

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| 76 | 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 | 3048350 |
| 77 | survival/ or cancer survival/ or survival rate/ or cancer specific survival/ or metastasis free survival/ or distant metastasis free survival/ or progression free survival/ or recurrence free survival/ or overall survival/ or local recurrence free survival/ | 519843 |
| 78 | recurrent disease/dm, dt, rt, si, su, th [Disease Management, Drug Therapy, Radiotherapy, Side Effect, Surgery, Therapy] | 8887 |
| 79 | (recurrence* or relapse*).ti,ab. | 400654 |
| 80 | "quality of life"/ or quality adjusted life year/ | 252636 |
| 81 | (quality adj life).ti,ab. | 418 |
| 82 | adverse event$.ti,ab. | 117391 |
| 83 | 77 or 78 or 79 or 80 or 81 or 82 | 1155294 |
| 84 | 17 and 48 and 76 and 83 | 618 |
| 85 | human tissue/ | 634745 |
| 86 | 84 not 85 | 604 |
| 87 | editorial/ | 479597 |
| 88 | letter/ | 811614 |
| 89 | note/ | 546616 |
| 90 | 87 or 88 or 89 | 1836418 |
| 91 | 86 not 90 | 541 |
| 92 | "review"/ | 1967246 |
| 93 | limit 91 to (human and english language) | 469 |
| 94 | "review"/ | 1967246 |
| 95 | 93 not 94 | 344 |

**Search strategies in HTA and NHSeed in CRD**

| | | |
|---|---|---|
| 1 | MeSH DESCRIPTOR Breast Neoplasms WITH QUALIFIERS DT, EC, MO, SU, RT, TH IN NHSEED,HTA | 440 |
| 2 | MeSH DESCRIPTOR Carcinoma, Ductal, Breast WITH QUALIFIERS DT, MO, EC, SU, TH, RTx IN NHSEED,HTA | 5 |
| 3 | (((Primary OR early stage OR early OR "stage I" OR "stage II" OR operable) ADJ1 (breast cancer OR breast cancers OR breast adenocarcinoma OR breast adenocarcinomas OR breast carcinomas OR breast carcinoma OR breast neoplasm OR breast neoplasms OR breast tumor OR breast tumour OR breast tumors OR breast tumours) )) IN NHSEED, HTA | 181 |
| 4 | #1 OR #2 OR #3 | 497 |
| 5 | MeSH DESCRIPTOR Breast Neoplasms WITH QUALIFIER GE IN NHSEED,HTA | 70 |
| 6 | MeSH DESCRIPTOR Breast Neoplasms WITH QUALIFIERS BS, BL, CF, CI, CH, CL, CO, CN, DI, DH, EC, EN, EP, EH, ETx, GE, HI, IM, ME, MI, NU, PS, PA, PP, RA, RI, RH, SC, US, UL, UR, VE, VI IN NHSEED,HTA | 491 |
| 7 | MeSH DESCRIPTOR Carcinoma, Ductal, Breast WITH QUALIFIER GE IN NHSEED,HTA | 2 |
| 8 | MeSH DESCRIPTOR Carcinoma, Ductal, Breast WITH QUALIFIERS BL, BS, CF, CI, CH, CL, CO, CN, DI, EM, EN, EP, | 7 |

| | | |
|---|---|---|
| | EH, ETx, GE, HI, IM, RTx, ME, MI, NU, PS, PA, PP, PC, PX, RA, RI, RH, SC, SE, US, UL, UR, VE, VI IN NHSEED,HTA | |
| 9 | MeSH DESCRIPTOR Neoplasms WITH QUALIFIER GE IN NHSEED,HTA | 8 |
| 10 | MeSH DESCRIPTOR gene expression EXPLODE ALL TREES IN NHSEED,HTA | 9 |
| 11 | MeSH DESCRIPTOR Gene Expression Profiling EXPLODE ALL TREES IN NHSEED,HTA | 41 |
| 12 | MeSH DESCRIPTOR Gene Expression Regulation EXPLODE ALL TREES IN NHSEED,HTA | 22 |
| 13 | MeSH DESCRIPTOR Gene Expression Regulation, Neoplastic EXPLODE ALL TREES IN NHSEED,HTA | 4 |
| 14 | MeSH DESCRIPTOR Genetic Structures EXPLODE ALL TREES IN NHSEED,HTA | 116 |
| 15 | MeSH DESCRIPTOR Genetic Testing EXPLODE ALL TREES IN NHSEED,HTA | 218 |
| 16 | MeSH DESCRIPTOR Tumor Markers, Biological EXPLODE ALL TREES IN NHSEED,HTA | 209 |
| 17 | MeSH DESCRIPTOR Granulocyte Colony-Stimulating Factor IN NHSEED,HTA | 116 |
| 18 | MeSH DESCRIPTOR Chemotherapy-Induced Febrile Neutropenia IN NHSEED,HTA | 0 |
| 19 | MeSH DESCRIPTOR Surgical Wound Infection EXPLODE ALL TREES IN NHSEED,HTA | 156 |
| 20 | MeSH DESCRIPTOR Bone Neoplasms EXPLODE ALL TREES IN NHSEED,HTA | 80 |
| 21 | MeSH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating EXPLODE ALL TREES IN NHSEED,HTA | 4 |
| 22 | #5 OR #7 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 | 393 |
| 23 | #4 NOT #22 | 437 |
| 101 | MeSH DESCRIPTOR mastectomy IN NHSEED,HTA | 46 |
| 102 | MeSH DESCRIPTOR Mastectomy, Radical EXPLODE ALL TREES IN NHSEED,HTA | 8 |
| 103 | MeSH DESCRIPTOR Mastectomy, Segmental EXPLODE ALL TREES IN NHSEED,HTA | 29 |
| 104 | MeSH DESCRIPTOR Mastectomy, Simple EXPLODE ALL TREES IN NHSEED,HTA | 2 |
| 105 | (((mastectom* OR operat* OR surgery OR surgical OR breast conserv* OR lumpectomy OR "wide local excision" OR segmentectom* OR mammectom* OR quadrantectom*)) ) IN NHSEED, HTA | 7457 |
| 106 | MeSH DESCRIPTOR Radiotherapy WITH QUALIFIERS EC, MO, AE IN NHSEED,HTA | 49 |
| 107 | MeSH DESCRIPTOR Brachytherapy EXPLODE ALL TREES WITH QUALIFIERS AE, EC, MO IN NHSEED,HTA | 19 |
| 108 | MeSH DESCRIPTOR Chemoradiotherapy EXPLODE ALL TREES WITH QUALIFIERS AE, EC, MO IN NHSEED,HTA | 3 |
| 109 | MeSH DESCRIPTOR Radiotherapy, Adjuvant EXPLODE ALL TREES WITH QUALIFIERS EC, AE, MO IN NHSEED,HTA | 13 |
| 110 | ((radiotherap* or brachytherap*) ) IN NHSEED, HTA | 595 |
| 111 | MeSH DESCRIPTOR Antineoplastic Agents, Hormonal WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 58 |
| 112 | MeSH DESCRIPTOR Tamoxifen WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 51 |

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|---|---|---|
| 113 | MeSH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 24 |
| 114 | MeSH DESCRIPTOR Breast Neoplasms IN NHSEED | 483 |
| 115 | MeSH DESCRIPTOR Carcinoma, Ductal, Breast IN NHSEED | 6 |
| 116 | MeSH DESCRIPTOR drug therapy WITH QUALIFIERS EC, MO, SN IN NHSEED,HTA | 38 |
| 117 | MeSH DESCRIPTOR Chemotherapy, Adjuvant IN NHSEED,HTA | 184 |
| 118 | MeSH DESCRIPTOR Chemotherapy, Adjuvant EXPLODE ALL TREES IN NHSEED,HTA | 184 |
| 119 | MeSH DESCRIPTOR Taxoids EXPLODE ALL TREES WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 117 |
| 120 | MeSH DESCRIPTOR Antimetabolites, Antineoplastic EXPLODE ALL TREES WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 45 |
| 121 | MeSH DESCRIPTOR Cyclophosphamide WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 57 |
| 122 | MeSH DESCRIPTOR Doxorubicin WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 57 |
| 123 | MeSH DESCRIPTOR Epirubicin EXPLODE ALL TREES WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 12 |
| 124 | MeSH DESCRIPTOR Methotrexate EXPLODE ALL TREES WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 48 |
| 125 | MeSH DESCRIPTOR Mitomycins WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 2 |
| 126 | MeSH DESCRIPTOR Fluorouracil WITH QUALIFIERS AD, AE, EC, TU, TO IN NHSEED,HTA | 84 |
| 127 | ((chemotherap* or cyclophosphamide or methotrexate or fluorouracil or doxorubicin or adriamycin or epirubicin or mitozantrone or mitomycin or paclitaxel or docetaxel)) IN NHSEED, HTA | 1547 |
| 128 | ((("endocrine therapy" OR "hormonal therapy" OR "endocrine therapies" OR "hormonal therapies" OR tamoxifen OR anastrozole OR letrozole OR exemestane OR "aromatase inhibitor" OR "aromatase inhibitors"))) IN NHSEED, HTA | 177 |
| 129 | MeSH DESCRIPTOR Antibodies, Monoclonal, Humanized WITH QUALIFIERS AD, AE, DE, EC, TU, TO IN NHSEED,HTA | 60 |
| 130 | #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 | 9135 |
| 131 | MeSH DESCRIPTOR Disease-Free Survival IN NHSEED,HTA | 164 |
| 132 | MeSH DESCRIPTOR Survival Analysis IN NHSEED,HTA | 528 |
| 133 | MeSH DESCRIPTOR Survival Rate IN NHSEED,HTA | 397 |
| 134 | MeSH DESCRIPTOR Survival EXPLODE ALL TREES IN NHSEED,HTA | 15 |
| 135 | MeSH DESCRIPTOR recurrence IN NHSEED,HTA | 460 |
| 136 | MeSH DESCRIPTOR Neoplasm Recurrence, Local WITH QUALIFIERS DT, EC, RTx, MO, SU, TH IN NHSEED,HTA | 63 |
| 137 | (recurrence* or relapse*) IN NHSEED, HTA | 1642 |

| | | |
|---|---|---|
| 138 | MeSH DESCRIPTOR Quality-Adjusted Life Years EXPLODE ALL TREES IN NHSEED,HTA | 2978 |
| 139 | MeSH DESCRIPTOR Quality of Life EXPLODE ALL TREES IN NHSEED,HTA | 1319 |
| 140 | ((survival OR death OR survive OR disease free survival OR recurrence free survival OR "metastasis free survival") ) IN NHSEED, HTA | 4753 |
| 141 | ((quality of life* OR quality adjusted life*)) IN NHSEED, HTA | 6806 |
| 142 | ((adverse event*)) IN NHSEED, HTA | 1583 |
| 143 | #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 | 10241 |
| 144 | #23 AND #130 AND #143 | 268 |

## Appendix 7. The economic checklists questions used to assess the quality of the 29 economic evaluation studies

| Quality assessment categories | Economic evaluation checklists questions | References |
|---|---|---|
| **Model structure** | | |
| 1 | The research question was presented | CHEERS |
| 2 | The relevance of the research question to decision-makers was described | CHEERS |
| 3 | The objective of the economic model was described | CHEERS |
| 4 | The characteristics of the target population were stated | CHEERS |
| 5 | The subgroup analyses were described and justified | CHEERS |
| 6 | The setting of health care was stated | CHEERS |
| 7 | The location of the economic evaluation perspective was stated | CHEERS |
| 8 | The perspective was stated and justified | CHEERS |
| 9 | The costs were relevant to the perspective | CHEERS |
| 10 | The scope of the model was stated and justified | Philips |
| 11 | Rationale for choosing the alternative treatments were stated | CHEERS |
| 12 | Alternative treatments were described | CHEERS |
| 13 | Type of economic evaluation considered was stated | CHEERS |
| 14 | The choice of the type of economic evaluation was justified | CHEERS |
| 15 | The model structure was consistent with the disease clinical course | Philips |
| 16 | The sources of data used to develop the model structure were specified | Philips |
| 17 | The structural assumptions used were transparent and justified | CHEERS |
| 18 | The model type was stated and justified | CHEERS |
| 19 | A figure for the model was provided | CHEERS |
| 20 | The time horizon was described and justified | CHEERS |
| 21 | Shorter lifetime horizon was justified | CHEERS |
| 22 | The disease states reflect disease pathways | Philips |
| 23 | Cycle length was defined and justified | CHEERS |
| **Data source** | | |
| 24 | The source of effectiveness was stated | CHEERS |
| 25 | Details of single study design were stated | CHEERS |
| 26 | A detailed method of synthesis, if data were combined from different sources, was stated | CHEERS |
| 27 | Selecting of appropriate data | CHEERS |
| 28 | Identify the data systematically | CHEERS |
| 29 | Quality of data assessed | CHEERS |
| 30 | Using of an expert opinion was justified | CHEERS |
| 31 | Baseline data was described and justified | Philips |
| 32 | Transition probabilities were calculated appropriately | CHEERS |

**(Continue Appendix 7.)**

| Quality assessment categories | Economic evaluation checklists questions | References |
|---|---|---|
| **Data source** | | |
| 33 | Half cycle correction was used | CHEERS |
| 34 | Treatment effect, if derived from trial data, was synthesised using meta-analysis | Philips |
| 35 | Method of extrapolation of short-term to long-term results was described and justified | CHEERS |
| 36 | Alternative assumptions regarding extrapolation were explored through sensitivity analysis | Philips |
| 37 | Assumptions regarding treatment benefit duration were reported and justified | Philips |
| 38 | Alternative assumptions for treatment benefit duration were explored and justified | Philips |
| 39 | Data not mutually consistent in terms of patients' characteristics were justified | Philips |
| 40 | Methods of data incorporation (i.e. as a point estimate or distribution) in the model were transparent | Philips |
| 41 | Choice of distribution for parameters were described and justified | CHEERS |
| 42 | Method of valuing health utilities was described | CHEERS |
| 43 | Population to elicit health utility value was described | CHEERS |
| 44 | Type of utility based measures were stated | CHEERS |
| 45 | Quantities of resources were reported separately from the unit cost | CHEERS |
| 46 | Method for estimation of quantities and unit costs were described | CHEERS |
| 47 | Currency and price data were reported | CHEERS |
| 48 | Adjustment for inflation was reported | CHEERS |
| 49 | Currency conversion was reported | CHEERS |
| 50 | Discount rates for cost and outcome were reported | CHEERS |
| 51 | Discount rates were justified | CHEERS |
| 52 | An explanation if discounting has not been used | CHEERS |
| 53 | The primary outcome measure was stated and justified | CHEERS |
| 54 | Values for study parameters were reported | CHEERS |
| 55 | Ranges for study parameters were reported | CHEERS |
| 56 | References for values and range were reported | CHEERS |
| 57 | Table for input parameters was provided | CHEERS |
| **Uncertainty** | | |
| 58 | Tornado diagram was provided for one-way sensitivity analysis | CHEERS |
| 59 | All types of uncertainties were reported | CHEERS |
| 60 | Methodological uncertainty was addressed | Philips |
| 61 | Structural uncertainty was reported | CHEERS |

**(Continue Appendix 7.)**

| Quality assessment categories | Economic evaluation checklists questions | References |
|---|---|---|
| **Uncertainty** | | |
| 62 | Heterogeneity was reported | CHEERS |
| 63 | Parameter uncertainty was addressed | CHEERS |
| 64 | Assessment of parameter uncertainty was appropriate | Philips |
| 65 | The method used for the assessment of the PSA was conducted | CHEERS |
| 66 | Lists of parameters used in the PSA and the use of CE and CEAC were presented | CHEERS |
| 67 | Variables used in the sensitivity analysis were justified | Philips |
| 68 | Point estimate used was described and justified | CHEERS |
| 69 | Internal consistency | Philips |
| 70 | Model calibrated against external data was described | Philips |
| **Results presentation and interpretation** | | |
| 71 | Incremental analysis was reported | CHEERS |
| 72 | Mean values of the estimated costs and outcomes for each comparator were reported | CHEERS |
| 73 | The differences in mean outcomes and costs were reported | CHEERS |
| 74 | The study results with previous results were compared | CHEERS |
| 75 | Key findings of the study were summarised | CHEERS |
| 76 | Generalisability of results to the clinical practice was reported | CHEERS |
| 77 | The limitations of the study were presented | CHEERS |
| 78 | Source of funding was reported | CHEERS |
| 79 | Conflict of interest was reported | CHEERS |

## Appendix 8. Reasons for excluding studies from the review of economic evaluations of different treatment strategies for women with primary breast cancer

| | Exclusion Criteria | Number of excluded studies |
|---|---|---|
| **Condition** | Metastatic breast cancer | 167 |
| | Locally advanced breast cancer | 10 |
| | Recurrence of breast cancer | 1 |
| | Unconfirmed breast cancer | 6 |
| | Non-invasive breast cancer | 4 |
| | Other diseases | 9 |
| **Population** | Male | 0 |
| | Premenopausal | 46 |
| **Intervention** | Diagnostic test to determine response | 34 |
| | Treating of cancer complication | 8 |
| | Preoperative treatment (neoadjuvant) | 16 |
| | Sociodemographic comparison (work, age, education, ethnicity) | 64 |
| | No comparators or interventions | 22 |
| | Prevalence and incidence of breast cancer | 1 |
| | Adherence | 10 |
| | Breast reconstruction | 18 |
| | Drug and treatment technology design | 54 |
| | Insurance coverage | 9 |
| | Nursing or exercise or rehabilitation care or psychological care | 29 |
| | Treatments or prevention for adverse drug events | 132 |
| | Health care and drug utilization | 14 |
| | Patient satisfaction | 5 |
| | Patient preferences | 8 |
| | Monitoring treatment effectiveness and adverse events | 6 |
| | Health care system related factor (communication with patients) | 1 |
| | Quality assurance | 1 |
| | Health care quality | 2 |
| | Procedures for diagnosis or staging of breast cancer | 98 |
| | Genetic test to determine response after treatment | 24 |
| | Head-to-head comparison | 142 |
| | Follow-up strategy (mammogram, hospital duration) | 27 |
| | Preventive strategy | 15 |

**(Continue Appendix 8.)**

| | Exclusion Criteria | Number of excluded studies |
|---|---|---|
| **Type of study** | Partial economic study | 62 |
| | Questionnaires | 21 |
| | Qualitative study | 29 |
| | Case study | 6 |
| | Statistical analysis | 4 |
| | literature review | 107 |
| | Case report | 0 |
| | Economic evaluation alongside RCT | 7 |
| | Systematic review | 8 |
| | Guideline | 8 |
| | Protocol | 1 |
| | Clinical trials | 55 |
| | Epidemiological study | 54 |
| | Cost minimisation analysis | 0 |
| | Pilot | 3 |
| **Type of publication** | Conference abstract | 41 |
| | Conference proceeding | 2 |
| | Commentary | 9 |
| | Summary | 1 |
| | Newspaper | 5 |
| | News | 15 |
| | Essay | 1 |
| | Editorial | 1 |
| **Language** | Non-English | 7 |

**Appendix 9. Model characteristics of the 29 included economic studies**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER / ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Campbell, 2011<br>40 years | 12 months<br>Yes<br>Lifetime | DF, LR, DR, contralateral tumour, death (BC or non-BC) | Aggregate/ disaggregate<br>Deterministic | Probabilistic analysis<br>One-way analysis | Area of uncertainty: PAS for key parameter (event probabilities, treatment effect, utility, cost)<br>One-way analysis (duration of treatment effects, time depend chemotherapy treatment effects).<br>Threshold analysis for doxetaxel price, CTx treatment effect duration<br>Source: Literature |
| Skedgel, 2013<br>40, 50, 60, and 70 years | 1 month<br>Yes<br>Lifetime | DF +/- cardiotoxicity, LR (LR or RR or contralateral tumour) +/- cardiotoxicity, RF after LR+/- cardiotoxicity, DR +/- cardiotoxicity, death | Aggregate only<br>Deterministic | Probabilistic analysis<br>One-way analysis | Area of uncertainty: PSA for cost, utility, and transition probabilities<br>One-way analysis :cost, Trz duration of benefit, treatment effect, utility, and discount rate<br>Not stated<br>Assumption |
| Kurian, 2007<br>49 years | 1 month<br>Yes<br>Not stated | RF, recurrence (didn't define any type of recurrence), CAT, CAT and recurrence, and death (any cause) | Aggregate/ disaggregate<br>Deterministic and probabilistic | Probabilistic analysis<br>One-way analysis | PSA: transition probabilities, treatment effect, utilities, and costs<br>One-way analysis: discount rate, treatment effect, utilities, and costs<br>Discount rate, cost of initial treatment, and cost of metastatictreatment<br>Literature |
| Shiroiwa, 2008<br>49 years | 1 month<br>No<br>Lifetime | RF, LR, DR, and death | Aggregate only<br>Deterministic | Probabilistic analysis<br>One-way analysis | PSA: transition probabilities, and cost<br>One-way analysis: discount rate, recurrence rate, cardiotoxicity rate, and terminal costs<br>Trz duration benefit, and discount rate<br>Not stated |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER / ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Skedgel, 2009<br>49 years | 1 month<br>Yes<br>25 years | DF +/- cardiotoxicity, LR (LR or RR or contralateral tumour) +/- cardiotoxicity, well after LR+/- cardiotoxicity, DR +/- cardiotoxicity,and death | Aggregate only<br>Probabilistic | One-way analysis<br>Probabilistic analysis<br>Threshold analysis | PSA: cost, utility, and transition proabilities<br>One-way analysis:cost, treatment effect, and discount rate<br>Threshold analysis: Trz duration of benefit<br>Costs, Trz duration of benefit and discount rate<br>Literature |
| Vlaenderen, 2009<br>50 years | 12 months<br>Yes<br>Lifetime | DF, local recurrence, DR, CAT, and death<br>Temporary state: LR or RR, DR, and DF during the first 5 years after treatment | Aggregate only<br>Probabilistic | Probabilistic analysis | PSA: cost, transition probabilities, and utility<br>NA<br>Literature |
| Dedes, 2007<br>50 years | 12 months<br>No<br>15 years | DF, RR, LR, DR, and death | Aggregate only<br>Deterministic | One-way analysis<br>Scenario analysis | One-way analysis: cost, and treatment effect<br>Scenario analysis: discount rate<br>Treatment efficacy, discounting of effectiveness, and prescription costs<br>Assumption, and literature |
| Liberato, 2007<br>50 years | 3 months<br>Yes<br>15 years | DF, LR, DF after LR, DR, and death | Aggregate/ disaggregate<br>Probabilistic | Multi-way analysis<br>Probabilistic analysis | PSA: treatment effect, transition probabilities, and cost<br>Multi-way:time horizon, age of patients, treatment effect, transition probabilities, and cost<br>Time horizon and age of patients<br>Literature |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER / ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Garrison, 2007<br>50 years | Not stated<br>Yes<br>Lifetime | Treatment, DFS, DR, and death | Aggregate only<br>Deterministic | One-way analysis<br>Multi-way analysis | Discount rate, transition probabilities, costs, and utilities<br>Discount rate, price of Trz, and probabilities of metastasis<br>Not stated |
| Millar, 2007<br>50 years | 12 months<br>Yes<br>Lifetime | DF,LR or RR, DR, death from MBC, and non-BC<br>BC or non-BC | Aggregate only<br>Deterministic | One-way analysis<br>Multi-way analysis | Discount rate, age at diagnose, efficacy, cost of Trz, variation in cost, of treating metastatic disease, duration of benefit of the Trz on disease recurrence<br>Initial acquisition costs, and duration of treatment benefit<br>Not stated |
| Chen, 2009<br>50 years | 12 months<br>No<br>Lifetime | DF, recurrence (LR and contralateral tumour), DR, CAT, death | Aggregate/disaggregate<br>Deterministic | One-way analysis | Discount rate, transition probabilities, and costs<br>Discounting rate of cost and LYG, probabilities of DFS progressed to recurrence and metastasis<br>Not stated |
| Purmonen, 2011<br>50 years | 1 month<br>Yes<br>Lifetime | No disease progression, distant progression, and death | Aggregate/disaggregate<br>Probabilistic | Probabilistic analysis<br>One-way analysis<br>Scenario analysis | PSA: transition probabilities, utility, costs,<br>One-way analysis: transition probabilities, costs, utilities, and discount rate<br>Scenario analysis: Trz benefit duration<br>Discount rate and Trz costs<br>Not stated |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER / ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Hedden, 2012<br>50 years | 3 months<br>Yes<br>28 years | Adj Trz, adj symptomatic CHF, adj CTx, RF, LR, non-progressive metastatic, metastatic symptomatic CHF, progressive metastatic, non-progressive metastatic (no Trz), death | Aggregate only<br>Deterministic | One-way analysis<br>Probabilistic analysis | PSA: Costs, utilities, treatment effect, transition probabilities<br>One-way analysis: Discount rate, cardiac toxicity probabilities, cost of Trz, and rate of relapse<br>Discount rate<br>Literature |
| Hall, 2011<br>50 years | 3 months<br>Yes<br>Lifetime | DF, symptomatic or asymptomatic CAT, recurrence (LRR or DR or contralateral tumour +/- CAT, DF after LR +/- CAT, death | Aggregate/ disaggregate<br>Probabilistic | One-way analysis<br>Probabilistic analysis<br>Multi-way analysis | PSA: transition probabilities, treatment effect, costs, and utilities<br>One-way analysis: transition probabilities, treatment effect, costs, and utilities, discount rate, and duration of benefit<br>Duration of treatment benefit, cost of Trz, hazard ratio, discount rate of benefit<br>Expert opinion |
| Bai, 2012<br>52 years | 1 month<br>Yes<br>Lifetime | RF, LR, DR, death from non-BC, death from BC | Aggregate/ disaggregate<br>Deterministic | One-way analysis<br>Probabilistic analysis<br>Scenario analysis | PSA: cost, utilities, transition probabilities, treatment effect<br>One-way analysis: age, cost, utility, treatment effect, and discount rate<br>Age at diagnosis of EBC<br>Other, including discount rate, cost of RTx, cost of managing future recurrence<br>Literature |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER/ ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Buendia, 2013<br>50 years | 12 months<br>Yes<br>Lifetime | DF, LR (LRR and contralateral tumour), DR, CAT, death from MBC, and death from non-BC | Aggregate/ disaggregate<br>Deterministic | Probabilistic analysis<br>One-way analysis | PSA: utility, transition probabilities, cost, treatment effect<br>One-way analysis: utility, discount rate, transition probabilities, cost, treatment effect, and Trz duration benefit<br>Discount rate and duration of Trz benefit<br>Not stated |
| Hillner, 1991<br>60 years | 12 months<br>Lifetime | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Aggregate only<br>Deterministic | Analysis of extremes | Treatment effect, utility, CTx benefit duration, and discount rate<br>CTx duration benefit<br>Not stated |
| Hillner, 1992 (a)<br>60 years | 12 months<br>Lifetime | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Aggregate only<br>Deterministic | Scenario analysis | Treatment duration benefit, treatment effect, and cost<br>CTx duration benefit, and treatment effect<br>Not stated |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER/ ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Hillner, 1992 (b)<br>60 years | 12 months<br>Lifetime | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Aggregate only<br>Deterministic | Not reported | Treatment duration benefit, treatment effect, and cost<br>Treatment duration benefit<br>Not stated |
| Hillner, 1993 (a)<br>60 years | 12 months<br>Yes<br>Lifetime | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Aggregate only<br>Deterministic | Not reported | CTx duration benefit, treatment effect, and cost, and discount rate<br>CTx duration benefit<br>Not stated |
| Hillner, 1993 (b)<br>60 years | Not stated<br>Lifetime | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Aggregate only<br>Deterministic | Not carried out | Not carried out<br>None<br>Not stated |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER/ ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| Hayman, 1998<br>60 years | 12 months<br>No<br>10 years | DF, LR, DR, death from BC, death from non-BC | Aggregate/ disaggregate<br>Deterministic | One-way analysis | Utilities, cost, treatment effect, and transition probabilities<br>Local recurrence rate, utility values of locally relapsed patients on RTx, costs of RTx<br>Not stated |
| Desch, 1993<br>60-80 years | Not stated<br>No<br>Lifetime | Complete response, CTx with minor toxicity, CTx with major toxicity, first recurrence, death | Aggregate only<br>Deterministic | Analysis of extremes | Treatment effect, risk of death, and toxicities<br>None<br>Not stated |
| Lievens, 2005<br>Not stated | 6 months<br>Yes<br>20 years | RF, LR or RR or DR, death of BC, and death of non-BC | Aggregate/ disaggregate<br>Deterministic | One-way analysis<br>Threshold analysis | Costs, transition probabilities, utilities, and discount rate<br>None<br>Not stated |
| **DES** | | | | | |
| Karnon, 2002<br><65 years | Not relevant<br>Yes<br>Not stated | DF, LR or RR, DF after LR or RR, DR, and death | Aggregate/ disaggregate<br>Probabilistic | Probabilistic analysis | Costs, utilities, and transition probabilities<br>NA<br>Literature |
| **Model Type not mentioned** | | | | | |
| Yang, 2010<br><=39, 40-49, >=50 years | Not relevant<br>Yes<br>10 years | RF, LRR, DR, contralateral tumour, and death | Aggregate only<br>Deterministic | One-way analysis | Discount rate<br>None<br>Assumption |

**(Continue Appendix 9.)**

| Author, year<br>Age | Cycle length<br>Graphical presentation<br>Time horizon | Disease states | ICER/ ICUR results' presentation | Type of sensitivity analysis | Area of uncertainty tested<br>Key parameters influence ICER<br>Source of range for sensitivity analysis |
|---|---|---|---|---|---|
| **Model type not mentioned** | | | | | |
| Norum, 2007<br>50 years | Not relevant<br>Yes<br>Not stated | Adj CTx/RTx Trz, follow up, heart failure, RF, DR, Paclitaxel/Tratuzumab , Vinorelbine, treatment of relapse, and death | Aggregate only<br>Deterministic | One-way analysis | One-way analysis: discount rate, cost of outpatients' treatments, travelling and Trz costs, production gain, and LYG<br>Production gain, discount rate, and Trz costs<br>Assumption |
| Naeim, 2005 (a)<br>65, 75, >85 years | Not relevant<br>No<br>Not stated | Not stated | Aggregate only<br>Deterministic | One-way analysis<br>Threshold analysis | Utility, costs, treatment efficacy and discount rate<br>Discount rate<br>Not stated |
| Naeim, 2005 (b)<br>65, 75, and 85 years | Not relevant<br>No<br>Not stated | Not stated | Aggregate only<br>Deterministic | One-way analysis<br>Threshold analysis | One-way analysis: discount rate, utility, and costs<br>Threshold analysis: CTx efficacy<br>Discount rate<br>Assumption |

**(Note)** DF: disease free; RF: relapse free; LR: local recurrence, DR: distant recurrence; LRR: locoregional recurrence; Adj: adjuvant; CTx: chemotherapy; RTx: radiotherapy; ICER: incremental cost-effectiveness ratio; RR: regional recurrence; Trz: trastuzumab; CAT: cardiotoxicity; MBC: metastatic breast cancer; BC: breast cancer; Not stated: not mentioned; CHF: congestive heart failure.

**Appendix 10. Resource use, cost, and benefit measurements of the 29 included economic studies**

| Author, year<br>Age<br>Economic study type | Effectiveness data<br>Effectiveness data source<br>Year of effectiveness data | Type of cost<br>Unit cost source<br>Price year | Resource use data<br>Resource use data source<br>Year of resource use data | Utility value measurements<br>Method of utility value evaluation<br>Respondents for evaluation<br>Age of respondents<br>Utility values source | Currency<br>Discount rate (costs, outcomes) |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Campbell, 2011<br>40 years<br>CUA | Survival data, recurrence data, and side effects<br>Meta analysis, three pragmatic trials, and hospital data<br>Not stated | DMC<br>Literature, national statistics, and expert opinion<br>2009 | Drugs or treatment, drug administration, treatment for drug adverse events, recurrence costs (treatment), doctors' visit, hospitalisation, monitoring test, mammographic surveillance<br>Published literature, retrospective medical record<br>Not stated | Generic preference instrument, EQ-5D<br>TTO<br>Population<br>40 years<br>Published literature | Pound sterling<br>3.5%<br>3.5% |
| Skedgel, 2013<br>40, 50, 60, and 70 years<br>CUA | Survival data, recurrence data, and side effects<br>Published literature<br>Not stated | DMC, DNMC<br>Literature<br>2011 | Drugs or treatment, test screening, drug administration, monitoring test, treatment for drug adverse events, recurrence costs (treatment)<br>Not stated<br>Not stated | Generic preference instrument, EQ-5D<br>TTO<br>Population<br>>18 years<br>Published literature | Canadian dollar<br>3%<br>3% |
| Kurian, 2007<br>49 years<br>CUA | Survival data, recurrence data, and side effects<br>Published RCTs<br>Not stated | DMC, IC<br>Literature<br>2005 | Drugs or treatment, drug administration, treatment for drug adverse events, monitoring test, recurrence costs (treatment)<br>Alongside clinical trial, hospital database<br>Not stated | Direct elicitation & SF-6D<br>SG & VAS & TTO<br>Health care professional & population<br>45-89 years<br>Published literature | US dollar<br>3%<br>3% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Shiroiwa, 2008<br>49 years<br>CEA | Recurrence and survival data<br>HERA trial and published trials<br>Not stated | DMC<br>National statistics<br>Not stated | Drugs or treatment, doctors' visit, mammographic surveillance, treatment for drug adverse events, recurrence costs (treatment)<br>Not stated<br>Not stated | NA<br>NA<br>NA<br>NA<br>NA | Euro<br>3%<br>3% |
| Skedgel, 2009<br>49 years<br>CUA | Survival data, recurrence data, and side effects<br>HERA trial, meta-analysis, and NSABP<br>Not stated | DMC, DNMC<br>Literature<br>2007 | Drugs or treatment, test screening, drug administration, recurrence costs (treatment), treatment for drug adverse events<br>Published literature<br>Not stated | Direct elicitation<br>VAS& SG<br>Health care professional & patients<br>Not stated<br>Published literature | Canadian dollar<br>3%<br>3% |
| Liberato, 2007<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>MA and Published RCTs<br>Not stated | DMC<br>Literature<br>Not stated | Drugs or treatment, monitering test, treatment for drug adverse events, recurrence costs (treatment), doctors' visit<br>Alongside clinical trial, guideline<br>Not stated | Direct elicitation<br>SG<br>Patients<br>55-70 years<br>Published literature | US dollar & euro<br>3%<br>3% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Dedes, 2007<br>50 years<br>CEA | Survival data, recurrence data, and side effects<br>HERA, FinHer trials and national statistic (life table)<br>Not stated | DMC<br>National statistics, literature<br>2006 | Drugs or treatment, drug administration, treatment for drug adverse events, recurrence costs (treatment), doctors' visit, hospitalisation, monitoring test, screening for adverse event (CHF, sonography)<br>Alongside clinical trial, retrospective medical record<br>Not stated | NA<br>NA<br>NA<br>NA<br>NA | Euro<br>3%<br>3% |
| Garrison, 2007<br>50 years<br>CUA | Recurrence and survival data<br>Meta-analysis of trials<br>Not stated | DMC, DNMC<br>Literature, estimation (expert opinion)<br>2006 | Drugs or treatment, screening for adverse event (CHF, sonography), treatment for drug adverse events, recurrence costs (treatment)<br>Alongside clinical trial<br>Not stated | Direct elicitation<br>VAS& SG<br>Health care professional & patients<br>Not stated<br>Estimation | US dollar<br>3%<br>3% |
| Millar, 2007<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>Published RCTs<br>Not stated | DMC<br>National statistics, medical insurance<br>2005 | Drugs or treatment, screening for adverse event (CHF, sonography), treatment for drug adverse events, recurrence costs (treatment)<br>Not stated<br>Not stated | Not stated<br>TTO & SG<br>Health care professional<br>Not stated<br>Published literature | Australian dollar<br>3%<br>3% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| Vlaenderen, 2009<br>50 years<br>CUA | Survival data, recurrence data, and side effects<br>Published literature and HERA trial<br>Not stated | DMC<br>National statistics<br>2005 | Hospitalisation, drugs or treatment, monitoring test, doctors' visit, treatment for drug adverse events, test screening<br>Hospital database, expert panel or opinion, published literature<br>2004 | Direct elicitation<br>TTO & SG<br>Health care professional<br>Not stated<br>Published literature | Not stated<br>3%<br>1.5% |
| Chen, 2009<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>HERA trial and literature<br>Not stated | DMC<br>Estimation (expert opinion),<br>Not stated | Drugs or treatment, doctors' visit, monitoring test, hospitalisation<br>Expert panel or opinion<br>Not stated | Direct elicitation<br>SG<br>Patients<br>Not stated<br>Published literature | US dollar<br>3%<br>No |
| Purmonen, 2011<br>50 years<br>CUA | Recurrence and survival data<br>FinHer trial, life table<br>Not stated | DMC<br>Hospital finance department<br>2008 | Drug administration, drugs or treatment<br>Not stated<br>Not stated | Generic preference instrument, EQ-5D<br>TTO<br>Patients<br>28-93 years<br>Published literature | Euro<br>3%<br>3% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Hall, 2011<br>50 years<br>CUA | Survival data, recurrence data, and side effects<br>HERA trial, life table from Office of National Statistics, and other published study<br>Not stated | DMC<br>National statistics, literature<br>2008 | Drugs or treatment, drug administration, screening for adverse event (CHF, sonography), doctors' visit, mammographic surveillance, treatment for drug adverse events, recurrence costs (treatment)<br>Guideline<br>2008 | EQ-5D & mapping<br>TTO<br>Patients<br>28-93 years<br>SR of literature | Pound sterling<br>3.5%<br>3.5% |
| Hedden, 2012<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>Clinical trials<br>Not stated | DMC<br>Literature, National statistics<br>2008 | Drugs or treatment, treatment for drug adverse events, screening for adverse event (CHF, sonography)<br>Published literature<br>2002-2007 | Not stated<br>TTO & SG<br>Health care professional<br>Not stated<br>SR of literature | Canadian dollar<br>5%<br>5% |
| Buendia, 2013<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>Published three clinical trials<br>Not stated | DMC<br>Literature<br>2010 | Drugs or treatment, test screening, drug administration, treatment for drug adverse events, recurrence costs (treatment)<br>Not stated<br>Not stated | Not stated<br>Not stated<br>Not stated<br>Not stated<br>Published literature | US dollar<br>5%<br>5% |

**(Continue Appendix 10.)**

| Author, year<br>Age<br>Economic study type | Effectiveness data<br>Effectiveness data source<br>Year of effectiveness data | Type of cost<br>Unit cost source<br>Price year | Resource use data<br>Resource use data source<br>Year of resource use data | Utility values measurements<br>Method of utility values evaluation<br>Respondents for evaluation<br>Age of respondents<br>Utility values source | Currency<br>Discount rate (costs, outcomes) |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Bai, 2012<br>52 years<br>CUA | Recurrence and survival data<br>Meta-analysis,published RCTs, and life table<br>Not stated | DMC, DNMC<br>Literature, estimation (expert opinion)<br>2012 | Drugs or treatment, recurrence costs (treatment), doctors' visit<br>Expert panel or opinion, published literature, assumption, clinical practice<br>Not stated | Generic preference instrument, EQ-5D<br>TTO<br>Patients<br>28-93 years<br>Published literature | US dollar<br>3%<br>3% |
| Hillner, 1991<br>60 years<br>CUA | Survival data, recurrence data, and side effects<br>Review of literature and expert opinions<br>Not stated | DMC<br>National statistics<br>1989 | Drugs or treatment, recurrence costs (treatment), hospitalisation, monitoring test, terminal care, staff cost<br>Not stated<br>Not stated | Not stated<br>Not stated<br>Health care professional<br>Not stated<br>Expert opinion | US dollar<br>5%<br>5% |
| Hillner, 1992<br>60 years<br>CUA | Survival data, recurrence data, and side effects<br>Review of clinical trials, Life table<br>Not stated | DMC<br>Estimation (expert opinion), Insitution or department statistic<br>1989 | Drugs or treatment, staff cost, recurrence costs (treatment), terminal care, monitoring test, hospitalisation<br>Hospital database<br>Not stated | Not stated<br>Not stated<br>Health care professional<br>Not stated<br>Expert opinion | US dollar<br>5%<br>5% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **Markov model** | | | | | |
| Hillner, 1992<br>60 years<br>CUA | Survival data, recurrence data, and side effects<br>Review of trials<br>Not stated | DMC<br>Estimation (expert opinion), Insitution or department statistics<br>Not stated | Drugs or treatment, recurrence costs (treatment), monitoring test, hospitalisation, terminal care, staff cost<br>Hospital database<br>1974-1981 | Not stated<br>Not stated<br>Health care professional<br>Not stated<br>Not stated | Not stated<br>5%<br>5% |
| Hillner, 1993<br>60 years<br>CUA | Survival data, recurrence data, and side effects<br>Meta-analysis<br>Not stated | DMC<br>National statistics<br>Not stated | Drugs or treatment, recurrence costs (treatment), staff cost, terminal care, monitoring test, hospitalisation<br>Hospital database<br>1974-1981 | Not stated<br>Not stated<br>Health care professional<br>Not stated<br>Expert opinion | US dollar<br>5%<br>5% |
| Hillner, 1993<br>60 years<br>CUA | Survival data, recurrence data, and side effects<br>Not stated<br>Not stated | DMC<br>Estimation (expert opinion), hospital finance department<br>Not stated | Drugs or treatment, doctors' visit, hospitalisation, monitoring test<br>Hospital database<br>1974-1981 | Not stated<br>Not stated<br>Health care professional<br>Not stated<br>Expert opinion | Not stated<br>5%<br>5% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **Model type not mentioned** | | | | | |
| Hayman, 1998<br>60 years<br>CUA | Recurrence and survival data<br>NSABP project (B01) and other RCTs<br>Not stated | DMC, DNMC<br>National statistics<br>1995 | Drugs or treatment, doctors' visit, drug administration, hospitalisation, staff cost<br>Clinical practice<br>Not stated | Direct elicitation<br>SG<br>Patients<br>Published literature | US dollar<br>3%<br>3% |
| Desch, 1993<br>60-80 years<br>CUA | Survival data, recurrence data, and side effects<br>Published RCTs<br>Not stated | DMC, DNMC, IC<br>National statistics<br>1990 | Drugs or treatment, treatment for drug adverse events<br>Not stated<br>Not stated | Not stated<br>Not stated<br>Not stated<br>Not stated | US dollar<br>5%<br>5% |
| Lievens, 2005<br>Not stated<br>CUA, CEA | Recurrence and survival data<br>Meta-analysis and published trials<br>Not stated | DMC, DNMC<br>Not stated<br>2000 | Drugs or treatment, hospitalisation, doctors' visit<br>Clinical practice<br>Not stated | Direct elicitation<br>TTO & SG<br>Not stated<br>Published literature | Euro<br>3%<br>3% |
| Yang, JJ, 2010<br>≤39, 40-49, ≥50 years<br>CEA | Survival data<br>Obsrevational study of 2nd database<br>1981-2005 | DMC, DNMC, IC<br>Medical insurance<br>2006 | Drugs or treatment, treatment for drug adverse events, recurrence costs (treatment), terminal care, screening for adverse event (CHF, sonography), doctors' visit<br>Guideline ; Not stated | NA<br>NA<br>NA<br>NA | US dollar<br>5%<br>5% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| Norum, 2007<br>50 years<br>CUA, CEA | Survival data, recurrence data, and side effects<br>Four trials<br>Not stated | DMC, DNMC, IC<br>National statistics, literature<br>2006 | Drugs or treatment, test screening, drug administration, treatment for drug adverse events, doctors' visit, screening for adverse event (CHF, sonography), hospitalisation<br>Guideline, alongside clinical trial<br>Not stated | Generic preference instrument, SF-6D<br>Not stated<br>Patients<br>30-90 years<br>SR of literature | Euro<br>3%<br>3% |
| Naeim, 2005<br>65, 75, >85 years<br>CUA | Survival data<br>Meta-analysis and life table<br>Not stated | DMC<br>National statistics<br>2001 | Drugs or treatment, doctors' visit, monitering test, drug administration<br>Published literature, guideline, expert panel or opinion<br>Not stated | Not stated<br>Health care professional<br>Not stated<br>Not stated | US dollar<br>3%<br>3% |
| Naeim, 2005<br>65, 75, and 85 years<br>CUA | Survival data<br>Meta-analysis and national statistic<br>Not stated | DMC<br>National statistics<br>2001 | Drugs or treatment, monitoring test, doctors' visit, drug administration, treatment for drug adverse events, hospitalisation<br>Published literature, guideline, expert panel or opinion<br>Not stated | Not stated<br>Not stated<br>Not stated<br>Not stated<br>SR of literature | US dollar<br>3%<br>3% |

**(Continue Appendix 10.)**

| **Author, year**<br>**Age**<br>**Economic study type** | **Effectiveness data**<br>**Effectiveness data source**<br>**Year of effectiveness data** | **Type of cost**<br>**Unit cost source**<br>**Price year** | **Resource use data**<br>**Resource use data source**<br>**Year of resource use data** | **Utility values measurements**<br>**Method of utility values evaluation**<br>**Respondents for evaluation**<br>**Age of respondents**<br>**Utility values source** | **Currency**<br>**Discount rate (costs, outcomes)** |
|---|---|---|---|---|---|
| **DES** | | | | | |
| Karnon, 2002<br><65 years<br>CUA | Survival data, recurrence data, and side effects<br>Published literature<br>Not stated | DMC<br>National statistics<br>2000 | Drugs or treatment, treatment for drug adverse events, drug administration, treatment for drug adverse events, recurrence costs (treatment)<br>Expert panel or opinion, published literature<br>Not stated | Direct elicitation<br>VAS<br>Health care professional<br>Not stated<br>Published literature | Pound sterling<br>6%<br>1.5% |

**(Note)** DMC: Direct medical cost; DNMC: Direct non-medical cost; IC: indirect cost; Euro: European; NA: not applicable; US: United States; QALY: quality adjusted life year; CHF: congestive heart failure; RCTs: randomized controlled trial; NC: not clear; SG: standard gamble; TTO: time trade off; VAS: visual analogue scale; EQ-5D: European Quality of Life-5 Dimensions; CUA: Cost utility analysis; CEA: Cost-effectivness analysis; SR: systematic review.

## Appendix 11. Quality assessment of the 29 included economic evaluation studies using Philip and CHEERS checklists

| Model structure | Q1: Research question | Q2: Relevance to decision-makers | Q3: Objective of model | Q4: Target | Q5: Subgroups/justified | Q6: Setting |
|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes | No | Yes | Yes/ No | No |
| Campbell, 2011 | Yes | Yes | No | Yes | Yes/ No | No |
| Chen, 2009 | NC | Yes | No | Yes | No/ NA | No |
| Hall, 2011 | Yes | Yes | No | Yes | No/ NA | No |
| Purmonen, 2011 | Yes | Yes | No | Yes | No/ NA | No |
| Yang, 2010 | Yes | No | No | Yes | Yes/ No | No |
| Buendia, 2013 | No | Yes | No | Yes | No/ NA | No |
| Naeim, 2005 | No | Yes | No | Yes | Yes/ No | No |
| Dedes, 2007 | Yes | Yes | No | Yes | No/ NA | No |
| Shiroiwa, 2008 | Yes | Yes | No | Yes | No/ NA | No |
| Norum, 2007 | No | Yes | Yes | Yes | No/ NA | NA |
| Naeim, 2005 | Yes | Yes | No | Yes | Yes/ No | No |
| Lievens, 2005 | Yes | Yes | No | Yes | No/ NA | Yes |
| Karnon, 2002 | Yes | Yes | No | Yes | No/ NA | No |
| Hayman, 1998 | Yes | Yes | No | Yes | No/ NA | No |
| Desch, 1993 | No | No | No | Yes | Yes/ No | No |
| Hillner, 1993 | Yes | No | No | Yes | No/ NA | No |
| Hillner, 1993 | No | No | No | Yes | Yes/ No | No |
| Hillner, 1992 | Yes | Yes | No | Yes | No/ NA | No |
| Hillner, 1992 | No | No | No | Yes | No/ NA | No |
| Hillner, 1991 | No | Yes | No | Yes | No/ NA | No |
| Skedgel, 2009 | Yes | Yes | No | Yes | No/ NA | No |
| Vlaenderen, 2009 | Yes | Yes | No | Yes | Yes/ No | No |
| Kurian, 2007 | Yes | Yes | No | No | No/ NA | No |
| Liberato, 2007 | Yes | Yes | No | Yes | No/ NA | No |
| Garrison, 2007 | Yes | Yes | No | Yes | No/ NA | No |
| Millar, 2007 | No | Yes | No | Yes | No/ NA | No |
| Skedgel, 2013 | Yes | Yes | No | Yes | No/ NA | No |
| Hedden, 2012 | Yes | Yes | No | Yes | No/ NA | No |

**(Continue Appendix 11.)**

| Model structure | Q7: Location | Q8: Perspective stated/justified | Q9: Costs relevant to perspective | Q10: Scope of model stated/ justified | Q11: Rationale for alternative | Q12: Alternative described |
|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes/No | No | Yes | No | No |
| Campbell, 2011 | Yes | Yes/No | NC | Yes/No | NC | No |
| Chen, 2009 | Yes | Yes/No | Yes | No | No | No |
| Hall, 2011 | Yes | Yes/No | Yes | No | No | No |
| Purmonen, 2011 | Yes | Yes/No | No | No | No | No |
| Yang, 2010 | Yes | Yes/No | Yes | No | No | No |
| Buendia, 2013 | Yes | Yes/No | Yes | No | No | No |
| Naeim, 2005 | No | No | NC | No | No | No |
| Dedes, 2007 | Yes | Yes/No | Yes | No | No | No |
| Shiroiwa, 2008 | Yes | Yes/No | Yes | No | No | No |
| Norum, 2007 | Yes | Yes/No | Yes | Yes/No | Yes | Yes |
| Naeim, 2005 | No | No | NC | No | No | No |
| Lievens, 2005 | Yes | Yes/No | No | No | No | No |
| Karnon, 2002 | Yes | Yes/No | Yes | No | No | No |
| Hayman, 1998 | Yes | Yes/No | Yes | No | No | No |
| Desch, 1993 | Yes | Yes/No | No | No | No | No |
| Hillner, 1993 | No | Yes/No | No | No | No | No |
| Hillner, 1993 | Yes | Yes/No | No | No | No | No |
| Hillner, 1992 | Yes | No | NC | No | No | Yes |
| Hillner, 1992 | No | No | NA | No | No | No |
| Hillner, 1991 | No | No | NA | No | No | No |
| Skedgel, 2009 | Yes | Yes/No | Yes | No | No | No |
| Vlaenderen, 2009 | Yes | Yes/No | Yes | No | No | No |
| Kurian, 2007 | Yes | Yes/No | Yes | Yes | No | Yes |
| Liberato, 2007 | Yes | Yes/No | Yes | No | No | No |
| Garrison, 2007 | Yes | Yes/No | No | No | No | No |
| Millar, 2007 | Yes | Yes/No | Yes | No | No | No |
| Skedgel, 2013 | Yes | Yes/No | Yes | No | No | Yes |
| Hedden, 2012 | Yes | Yes/No | Yes | No | No | No |

**(Continue Appendix 11.)**

| Model structure | Q13: Type of EE stated | Q14: Choice of EE justified | Q15: Model structure consistent with evidence | Q16: Source of data to develop structure specified | Q17: Structural assumption transparent and justified | Q18: Model type stated/justified |
|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | No | NC | No | Yes | Yes/No |
| Campbell, 2011 | Yes | No | NC | No | Yes/No | Yes/No |
| Chen, 2009 | Yes | No | NC | No | Yes/No | Yes/No |
| Hall, 2011 | Yes | No | Yes | Yes | Yes/No | Yes |
| Purmonen, 2011 | Yes | No | NC | No | Yes/No | Yes/No |
| Yang, 2010 | Yes | No | Yes | Yes | Yes/No | No |
| Buendia, 2013 | Yes | No | NC | No | Yes/No | Yes/No |
| Naeim, 2005 | Yes | No | NC | No | Yes/No | No |
| Dedes, 2007 | Yes | No | NC | No | Yes | Yes/No |
| Shiroiwa, 2008 | Yes | Yes | Yes | Yes | Yes/No | Yes/No |
| Norum, 2007 | Yes | No | NC | No | No | No |
| Naeim, 2005 | Yes | No | NC | No | Yes | No |
| Lievens, 2005 | Yes | No | NC | No | Yes/No | Yes/No |
| Karnon, 2002 | Yes | Yes | NC | No | Yes | Yes |
| Hayman, 1998 | Yes | Yes | No | Yes | Yes | Yes/No |
| Desch, 1993 | Yes | No | NC | No | Yes/No | Yes/No |
| Hillner, 1993 | No | No | NC | No | Yes/No | Yes |
| Hillner, 1993 | Yes | No | NC | No | Yes/No | Yes |
| Hillner, 1992 | Yes | No | NC | No | Yes/No | Yes |
| Hillner, 1992 | Yes | No | NC | No | Yes/No | No |
| Hillner, 1991 | Yes | No | NC | No | Yes | Yes |
| Skedgel, 2009 | Yes | No | NC | No | Yes/No | Yes/No |
| Vlaenderen, 2009 | Yes | No | NC | No | Yes/No | Yes/No |
| Kurian, 2007 | Yes | No | NC | No | Yes | Yes/No |
| Liberato, 2007 | Yes | No | NC | No | Yes/No | Yes/No |
| Garrison, 2007 | Yes | Yes | NC | No | Yes/No | Yes/No |
| Millar, 2007 | No | No | NC | No | Yes/No | No |
| Skedgel, 2013 | Yes | No | NC | No | Yes/No | Yes/No |
| Hedden, 2012 | Yes | No | No | No | No | Yes/No |

**(Continue Appendix 11.)**

| Model structure | Q19: Provide figure for the model | Q20: Time horizon described/justified | Q21: Lifetime not used, justified | Q22: Disease states reflect disease pathways | Q23: Cycle length defined/justified |
|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes/ Yes | NA | NC | Yes/No |
| Campbell, 2011 | Yes | No/ No | No | NC | Yes/No |
| Chen, 2009 | Yes | Yes/ No | NA | NC | Yes/No |
| Hall, 2011 | Yes | Yes/ Yes | NA | Yes | Yes/No |
| Purmonen, 2011 | Yes | Yes/ No | NA | NC | Yes/No |
| Yang, 2010 | Yes | No/ No | No | Yes | NA |
| Buendia, 2013 | Yes | No/ No | No | NC | Yes/No |
| Naeim, 2005 | No | No/ No | No | NA | No |
| Dedes, 2007 | No | Yes/ Yes | NA | NC | Yes/No |
| Shiroiwa, 2008 | Yes | Yes/ Yes | NA | Yes | Yes/No |
| Norum, 2007 | No | No/ No | No | NC | NA |
| Naeim, 2005 | No | No/ No | No | NA | NA |
| Lievens, 2005 | Yes | No/ No | No | NC | Yes/No |
| Karnon, 2002 | Yes | No/ No | No | NC | NA |
| Hayman, 1998 | No | No/ No | Yes | NC | Yes/No |
| Desch, 1993 | No | Yes/ No | No | NC | No |
| Hillner, 1993 | Yes | Yes/ No | NA | NC | Yes/No |
| Hillner, 1993 | Yes | Yes/ No | NA | NC | NA |
| Hillner, 1992 | Yes | Yes/ Yes | NA | NC | Yes/No |
| Hillner, 1992 | Yes | Yes/ Yes | NA | NC | Yes/No |
| Hillner, 1991 | Yes | Yes/ No | NA | No | Yes/No |
| Skedgel, 2009 | Yes | Yes/ Yes | NA | NC | Yes/No |
| Vlaenderen, 2009 | No | Yes/ Yes | NA | NC | Yes/No |
| Kurian, 2007 | Yes | Yes/ No | NA | NC | Yes/No |
| Liberato, 2007 | Yes | No/ No | No | NC | Yes/No |
| Garrison, 2007 | Yes | Yes/ Yes | NA | NC | No |
| Millar, 2007 | Yes | Yes/ Yes | NA | NC | Yes/No |
| Skedgel, 2013 | Yes | Yes/ No | NA | NC | Yes/No |
| Hedden, 2012 | Yes | Yes/No | NA | NC | Yes/No |

**(Continue Appendix 11.)**

| Data source and costs | Q24: Source of effectiveness | Q25: Details of study design | Q26: Detailed method of synthesis | Q27: Selecting of data | Q28: Identify data systematically | Q29: Quality of data assesssed | Q30: Expert opinion used, justified |
|---|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | NA | No | Yes | Yes | No | NA |
| Campbell, 2011 | Yes | No | No | No | Yes | No | NA |
| Chen, 2009 | Yes | NA | Yes | No | No | No | NA |
| Hall, 2011 | Yes | No | No | Yes | No | No | NA |
| Purmonen, 2011 | Yes | No | NA | No | No | No | NA |
| Yang, 2010 | Yes | Yes | NA | Yes | No | Yes | NA |
| Buendia, 2013 | Yes | NA | No | No | No | No | NA |
| Naeim, 2005 | Yes | NA | No | Yes | No | No | NA |
| Dedes, 2007 | Yes | NA | No | No | No | No | NA |
| Shiroiwa, 2008 | Yes | No | NA | No | Yes | No | NA |
| Norum, 2007 | Yes | NA | No | Yes | No | No | NA |
| Naeim, 2005 | Yes | NA | No | No | No | No | NA |
| Lievens, 2005 | Yes | NA | No | Yes | No | No | NA |
| Karnon, 2002 | Yes | NA | No | Yes | No | Yes | NA |
| Hayman, 1998 | Yes | No | NA | Yes | No | Yes | NA |
| Desch, 1993 | Yes | NA | No | No | No | No | NA |
| Hillner, 1993 | No | NA | NA | No | No | No | NA |
| Hillner, 1993 | Yes | NA | No | No | No | No | NA |
| Hillner, 1992 | NC | NA | No | No | No | No | NA |
| Hillner, 1992 | Yes | NA | NA | No | No | No | NA |
| Hillner, 1991 | Yes | NA | No | No | No | No | NA |
| Skedgel, 2009 | Yes | NA | No | Yes | No | No | NA |
| Vlaenderen, 2009 | Yes | NA | No | No | No | No | NA |
| Kurian, 2007 | Yes | NA | No | No | No | No | NA |
| Liberato, 2007 | Yes | NA | No | No | No | No | NA |
| Garrison, 2007 | Yes | NA | No | No | Yes | No | NA |
| Millar, 2007 | Yes | No | No | No | No | No | NA |
| Skedgel, 2013 | Yes | NA | No | No | No | No | NA |
| Hedden, 2012 | Yes | NA | No | No | No | No | NA |

**(Continue Appendix 11.)**

| Data source and costs | Q31: Baseline data described/justified | Q32: Transition probabilities calculated appropriately | Q33: Half cycle correction | Q34: Treatment effect synthesised | Q35: Method of extrapolation short term results/justified | Q36: Alternative assumptions explored for extrapolation | Q37: Assumptions of treatment duration reported and justified |
|---|---|---|---|---|---|---|---|
| Bai, 2012 | Yes/No | NA | No | Yes | Yes/No | No | Yes/No |
| Campbell,2011 | Yes/No | NA | No | Yes | Yes | No | Yes/No |
| Chen, 2009 | Yes/No | NA | No | NA | No | NA | Yes/No |
| Hall, 2011 | Yes | NA | Yes | NA | No | No | Yes |
| Purmonen, 2011 | Yes/No | NA | No | NA | Yes | No | Yes |
| Yang, 2010 | Yes | NA | NA | NA | No | NA | No |
| Buendia, 2013 | Yes/No | NA | No | No | No | NA | Yes/No |
| Naeim, 2005 | No | NA | No | Yes | No | NA | No |
| Dedes, 2007 | No | NA | No | No | No | NA | Yes |
| Shiroiwa, 2008 | Yes/No | NA | No | No | No | NA | Yes |
| Norum, 2007 | No | NA | No | No | No | NA | No |
| Naeim, 2005 | Yes/No | NA | No | Yes | No | No | No |
| Lievens, 2005 | Yes/No | NA | No | Yes | No | NA | No |
| Karnon, 2002 | Yes/No | NA | No | Yes | No | NA | No |
| Hayman, 1998 | Yes | NA | No | NA | No | NA | No |
| Desch, 1993 | Yes/No | NA | No | No | No | NA | No |
| Hillner, 1993 | No | NA | No | NA | No | NA | Yes |
| Hillner, 1993 | Yes/No | NA | No | Yes | No | NA | Yes |
| Hillner, 1992 | No | NA | No | No | No | NA | Yes |
| Hillner, 1992 | Yes/No | NA | No | NC | No | NA | Yes |
| Hillner, 1991 | No | NA | No | No | No | NA | Yes |
| Skedgel, 2009 | Yes/No | NA | No | No | No | NA | Yes |
| Vlaenderen, 2009 | Yes/No | NA | No | No | Yes/No | NA | Yes/No |
| Kurian, 2007 | Yes/No | NA | No | Yes | Yes | No | Yes |
| Liberato, 2007 | Yes/No | NA | No | Yes | No | NA | Yes |
| Garrison, 2007 | No | NA | No | Yes | Yes/No | NA | Yes/No |
| Millar, 2007 | Yes/No | NA | No | No | No | NA | Yes |
| Skedgel, 2013 | Yes/No | NA | No | Yes | No | NA | Yes |
| Hedden, 2012 | Yes/No | NA | No | No | No | NA | No |

**(Continue Appendix 11.)**

| Data source and costs | Q38: Alternative assumption for treatment duration explored | Q39: Data not mutually consistent justified | Q40: Data incorporation transparent | Q41: Choice of distribution for parameters described and justified | Q42: Method to value health utilities | Q43: Population elicit preferences | Q44: Type of utility based measures |
|---|---|---|---|---|---|---|---|
| Bai, 2012 | No | Yes | Yes | Yes/No | No | No | No |
| Campbell, 2011 | Yes | NA | Yes | Yes | Yes | Yes | Yes |
| Chen, 2009 | No | No | Yes | No | No | No | NA |
| Hall, 2011 | Yes | NA | Yes | Yes | Yes | Yes | Yes |
| Purmonen, 2011 | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Yang, 2010 | NA | NA | No | No | NA | NA | NA |
| Buendia, 2013 | Yes | NA | Yes | No | No | No | No |
| Naeim, 2005 | NA | NA | No | No | No | No | No |
| Dedes, 2007 | Yes | NA | Yes | No | NA | NA | NA |
| Shiroiwa, 2008 | Yes | NA | Yes | Yes | No | No | No |
| Norum, 2007 | NA | NA | No | No | No | No | No |
| Naeim, 2005 | No | Yes | No | No | No | No | No |
| Lievens, 2005 | NA | Yes | No | No | No | No | Yes |
| Karnon, 2002 | NA | NA | Yes | Yes | No | No | No |
| Hayman, 1998 | NA | NA | No | No | Yes | Yes | No |
| Desch, 1993 | NA | NA | Yes | No | No | No | No |
| Hillner, 1993 | No | NA | No | No | No | Yes | No |
| Hillner, 1993 | No | NA | No | No | No | No | No |
| Hillner, 1992 | Yes | NA | No | No | No | Yes | No |
| Hillner, 1992 | No | NA | No | No | No | Yes | No |
| Hillner, 1991 | No | NA | Yes | No | No | Yes | No |
| Skedgel, 2009 | Yes | NA | Yes | Yes | No | No | No |
| Vlaenderen, 2009 | No | NA | Yes | Yes | No | No | No |
| Kurian, 2007 | No | NA | Yes | No | Yes | No | No |
| Liberato, 2007 | No | NA | Yes | Yes | No | No | NA |
| Garrison, 2007 | No | NA | Yes | NA | No | No | No |
| Millar, 2007 | Yes | NA | No | No | No | No | No |
| Skedgel, 2013 | Yes | NA | Yes | Yes | No | No | No |
| Hedden, 2012 | No | NA | Yes | Yes | Yes | No | No |

**(Continue Appendix 11.)**

| Data source and costs | Q45: Quantities of resources reported seprately from unit cost | Q46: Method for estimation of quantities and unit costs described | Q47: Currency and price data reported | Q48: Adjustment for inflation | Q49: Currency conversion | Q50: Discount rate cost/outcome | Q51: Discount rate justified |
|---|---|---|---|---|---|---|---|
| Bai, 2012 | No | No | Yes | NA | NA | Yes/ Yes | No |
| Campbell, 2011 | Yes | Yes | Yes | No | NA | Yes/ Yes | No |
| Chen, 2009 | No | Yes | Yes/ No | No | No | Yes/ No | No |
| Hall, 2011 | No | Yes | Yes | No | NA | Yes/ Yes | No |
| Purmonen, 2011 | No | Yes | Yes | No | NA | Yes/ Yes | Yes |
| Yang, 2010 | No | Yes | Yes | NA | No | Yes/ Yes | No |
| Buendia, 2013 | No | No | Yes | No | NA | Yes/ Yes | No |
| Naeim, 2005 | No | Yes | Yes | NA | NA | Yes/ Yes | No |
| Dedes, 2007 | No | Yes | Yes | Yes | NA | Yes/ Yes | No |
| Shiroiwa, 2008 | No | Yes | Yes/ No | Yes | Yes | Yes/ Yes | No |
| Norum, 2007 | Yes | Yes | Yes | No | Yes | Yes/ Yes | Yes |
| Naeim, 2005 | NA | Yes | Yes | No | NA | Yes/ Yes | No |
| Lievens, 2005 | No | Yes | Yes | NA | NA | Yes/ Yes | No |
| Karnon, 2002 | No | Yes | Yes | NA | NA | Yes/ Yes | No |
| Hayman, 1998 | No | Yes | Yes | NA | NA | Yes/ Yes | No |
| Desch, 1993 | No | No | Yes | NA | NA | Yes/ Yes | No |
| Hillner, 1993 | No | Yes | No | No | NA | Yes/ Yes | No |
| Hillner, 1993 | No | Yes | No | No | NA | Yes/ Yes | No |
| Hillner, 1992 | No | Yes | Yes | No | NA | Yes/ Yes | No |
| Hillner, 1992 | No | Yes | No | No | NA | Yes/ Yes | No |
| Hillner, 1991 | No | Yes | Yes | NA | NC | Yes/ Yes | No |
| Skedgel, 2009 | No | Yes | Yes | NA | Yes | Yes/ Yes | No |
| Vlaenderen, 2009 | No | Yes | No | Yes | NA | Yes/ Yes | No |
| Kurian, 2007 | No | Yes | Yes | NA | NA | Yes/ Yes | No |
| Liberato, 2007 | Yes | Yes | Yes/ No | NA | NA | Yes/ Yes | Yes |
| Garrison, 2007 | No | Yes | Yes | No | NA | Yes/ Yes | Yes |
| Millar, 2007 | Yes | No | Yes | NA | NA | Yes/ Yes | No |
| Skedgel, 2013 | No | Yes | Yes | NA | Yes | Yes/ Yes | No |
| Hedden, 2012 | No | Yes/ No | Yes | No | NA | Yes/ Yes | No |

**(Continue Appendix 11.)**

| Data source and costs | Q52: Explanation if not discounted | Q53: Primary outcome stated/justified | Q54: Values for study parameters | Q55: Range for study parameters | Q56: Reference for values and range | Q57: Table for input parameters |
|---|---|---|---|---|---|---|
| Bai, 2012 | NA | Yes/ No | Yes | Yes | Yes | Yes |
| Campbell, 2011 | NA | Yes/ No | Yes | Yes | Yes | Yes |
| Chen, 2009 | No | Yes/ No | No | Yes | Yes | Yes |
| Hall, 2011 | NA | Yes | Yes | Yes | Yes | Yes |
| Purmonen, 2011 | NA | Yes | Yes | Yes | Yes | Yes |
| Yang, 2010 | NA | No/ No | Yes | Yes | Yes | Yes |
| Buendia, 2013 | No | Yes/ No | Yes | Yes | Yes | Yes |
| Naeim, 2005 | NA | Yes/ No | Yes/No | No | No | No |
| Dedes, 2007 | NA | Yes/ No | Yes | No | Yes | Yes |
| Shiroiwa, 2008 | NA | Yes/ No | Yes | No | Yes | Yes |
| Norum, 2007 | NA | Yes/ No | Yes/No | No | No | No |
| Naeim, 2005 | NA | No | No | No | No | No |
| Lievens, 2005 | NA | Yes/ No | Yes | No | Yes | Yes |
| Karnon, 2002 | NA | Yes/ No | No | No | No | No |
| Hayman, 1998 | NA | Yes/ No | Yes | No | Yes | Yes |
| Desch, 1993 | NA | Yes/ No | Yes | Yes | Yes/No | Yes |
| Hillner, 1993 | NA | No | No | No | No | No |
| Hillner, 1993 | No | Yes/ No | No | No | No | No |
| Hillner, 1992 | NA | Yes/ No | No | No | No | No |
| Hillner, 1992 | No | Yes/ No | No | No | No | No |
| Hillner, 1991 | NA | Yes/ No | No | No | No | No |
| Skedgel, 2009 | NA | Yes/ No | Yes | Yes | Yes | Yes |
| Vlaenderen, 2009 | No | Yes/ No | Yes | Yes | Yes | Yes |
| Kurian, 2007 | NA | Yes/ No | Yes | Yes | Yes | Yes |
| Liberato, 2007 | NA | Yes/ No | Yes | No | Yes | Yes |
| Garrison, 2007 | NA | Yes | Yes | Yes | Yes | Yes |
| Millar, 2007 | NA | Yes/ No | Yes | No | Yes | No |
| Skedgel, 2013 | NA | Yes/ No | Yes | Yes | Yes | Yes |
| Hedden, 2012 | NA | Yes/ No | Yes | Yes/No | Yes | Yes |

**(Continue Appendix 11.)**

| Uncertainty | Q58: Tornado diagram | Q59: Types of uncertainty reported | Q60: Methodological uncertainty | Q61: Structural uncertainty | Q62: Heterogeneity | Q63: Parameter uncertainty | Q64: Assessment of parameter uncertainty |
|---|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Campbell, 2011 | No | No | No | Yes | Yes | Yes | Yes |
| Chen, 2009 | Yes | No | Yes | No | No | No | No |
| Hall, 2011 | Yes | No | Yes | No | No | Yes | Yes |
| Purmonen, 2011 | No | No | Yes | Yes | No | Yes | Yes |
| Yang, 2010 | Yes | No | Yes | No | Yes | NA | No |
| Buendia, 2013 | No | No | Yes | Yes | No | Yes | Yes |
| Naeim, 2005 | No | No | Yes | No | No | No | No |
| Dedes, 2007 | No | No | Yes | Yes | No | No | No |
| Shiroiwa, 2008 | Yes | No | Yes | Yes | No | Yes | Yes |
| Norum, 2007 | Yes | No | Yes | No | No | No | No |
| Naeim, 2005 | No | No | Yes | No | Yes | No | No |
| Lievens, 2005 | No | No | Yes | Yes | No | No | No |
| Karnon, 2002 | No | No | No | No | No | Yes | Yes |
| Hayman, 1998 | Yes | No | No | No | No | NA | No |
| Desch, 1993 | No | No | No | No | Yes | No | No |
| Hillner, 1993 | NA | No | No | No | No | No | No |
| Hillner, 1993 | No | No | No | No | No | No | No |
| Hillner, 1992 | No | No | No | No | No | NC | No |
| Hillner, 1992 | No | No | No | No | No | No | No |
| Hillner, 1991 | No | No | Yes | Yes | No | No | No |
| Skedgel, 2009 | No | No | Yes | Yes | No | Yes | Yes |
| Vlaenderen, 2009 | No | No | No | No | Yes | NA | Yes |
| Kurian, 2007 | Yes | No | Yes | No | No | No | Yes |
| Liberato, 2007 | No | No | No | Yes | Yes | Yes | Yes |
| Garrison, 2007 | Yes | No | Yes | No | No | No | No |
| Millar, 2007 | No | No | Yes | Yes | Yes | No | No |
| Skedgel, 2013 | No | No | No | No | Yes | Yes | Yes |
| Hedden, 2012 | No | No | Yes | No | No | Yes | Yes |

**(Continue Appendix 11.)**

| Uncertainty | Q65: Probabilistic sensitivity analysis | Q66: List of parameters in PSA, CE, CEAC | Q67: Variable for sensitivity analysis justified | Q68: Point estimate described and justified | Q69: Internal consistency | Q70: Model calibrated justified |
|---|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes | No | No | No | Yes |
| Campbell, 2011 | Yes | Yes | No | No | No | NA |
| Chen, 2009 | No | NA | Yes/No | No | No | NA |
| Hall, 2011 | Yes | No | Yes | No | No | NA |
| Purmonen, 2011 | Yes | Yes | No | No | No | NA |
| Yang, 2010 | No | NA | No | No | No | NA |
| Buendia, 2013 | Yes | Yes/No | No | No | Yes | Yes |
| Naeim, 2005 | No | NA | No | No | No | Yes |
| Dedes, 2007 | No | NA | Yes | No | No | Yes |
| Shiroiwa, 2008 | Yes | Yes | NA | No | No | NA |
| Norum, 2007 | No | NA | No | No | No | NA |
| Naeim, 2005 | No | NA | No | No | No | NA |
| Lievens, 2005 | No | NA | No | No | No | Yes |
| Karnon, 2002 | Yes | Yes | No | Yes | Yes | Yes |
| Hayman, 1998 | No | NA | No | No | No | NA |
| Desch, 1993 | No | NA | Yes/No | No | No | NA |
| Hillner, 1993 | No | NA | No | No | No | NA |
| Hillner, 1993 | No | NA | NA | NA | No | NA |
| Hillner, 1992 | No | NA | NA | No | No | NA |
| Hillner, 1992 | No | NA | No | No | No | NA |
| Hillner, 1991 | No | NA | Yes/No | No | No | NA |
| Skedgel, 2009 | Yes | Yes/No | No | No | No | Yes |
| Vlaenderen, 2009 | Yes | Yes | No | No | No | NA |
| Kurian, 2007 | Yes | No | No | No | No | NA |
| Liberato, 2007 | Yes | No | NA | No | No | NA |
| Garrison, 2007 | No | NA | Yes/No | No | No | NA |
| Millar, 2007 | No | NA | No | No | No | Yes |
| Skedgel, 2013 | Yes | Yes | NA | No | No | NA |
| Hedden, 2012 | Yes | Yes | No | No | No | NA |

**(Continue Appendix 11.)**

| Results presentation and interpretation | Q71: Incremental analysis reported | Q72: Mean values of costs and outcomes | Q73: Difference in mean and outcomes | Q74: Compare with previous results | Q75: Summarise key findings |
|---|---|---|---|---|---|
| Bai, 2012 | Yes | Yes | Yes | Yes | Yes |
| Campbell, 2011 | Yes | Yes | Yes | No | Yes |
| Chen, 2009 | Yes | Yes | Yes | Yes | Yes |
| Hall, 2011 | Yes | Yes | Yes | Yes | No |
| Purmonen, 2011 | Yes | Yes | Yes | Yes | Yes |
| Yang, 2010 | Yes | No | No | No | Yes |
| Buendia, 2013 | Yes | Yes | Yes | Yes | Yes |
| Naeim, 2005 | Yes | No | No | Yes | No |
| Dedes, 2007 | Yes | No | Yes | Yes | Yes |
| Shiroiwa, 2008 | Yes | No | No | Yes | No |
| Norum, 2007 | Yes | No | No | Yes | No |
| Naeim, 2005 | Yes | No | No | No | No |
| Lievens, 2005 | Yes | Yes | Yes | Yes | No |
| Karnon, 2002 | Yes | Yes | No | No | No |
| Hayman, 1998 | Yes | Yes | Yes | Yes | Yes |
| Desch, 1993 | Yes | No | No | No | Yes |
| Hillner, 1993 | Yes | No | No | No | No |
| Hillner, 1993 | Yes | No | No | No | No |
| Hillner, 1992 | Yes | No | No | No | No |
| Hillner, 1992 | Yes | No | No | No | No |
| Hillner, 1991 | Yes | No | No | No | No |
| Skedgel, 2009 | Yes | No | No | Yes | Yes |
| Vlaenderen, 2009 | Yes | No | Yes | Yes | Yes |
| Kurian, 2007 | Yes | Yes | No | No | Yes |
| Liberato, 2007 | Yes | Yes | Yes | No | Yes |
| Garrison, 2007 | Yes | Yes | Yes | Yes | Yes |
| Millar, 2007 | Yes | No | No | No | Yes |
| Skedgel, 2013 | Yes | No | No | No | No |
| Hedden, 2012 | Yes | No | No | NA | Yes |

**(Continue Appendix 11.)**

| Results presentation and interpretation | Q76: Generalisability of results | Q77: The limitations presented | Q78: Source of fundings | Q79: Conflict of interest |
|---|---|---|---|---|
| Bai, 2012 | No | Yes | Yes | Yes/No |
| Campbell, 2011 | Yes/No | Yes | Yes | Yes/No |
| Chen, 2009 | No | Yes | Yes | Yes |
| Hall, 2011 | No | NC | Yes | Yes/No |
| Purmonen, 2011 | No | No | Yes | Yes/No |
| Yang, 2010 | No | Yes | Yes | Yes/No |
| Buendia, 2013 | Yes/No | Yes | Yes/No | Yes/No |
| Naeim, 2005 | No | Yes | Yes | No |
| Dedes, 2007 | No | Yes | No | Yes/No |
| Shiroiwa, 2008 | No | Yes | Yes | No |
| Norum, 2007 | No | No | Yes | NA |
| Naeim, 2005 | No | Yes | Yes | NA |
| Lievens, 2005 | No | Yes | No | No |
| Karnon, 2002 | No | Yes | Yes | No |
| Hayman, 1998 | No | Yes | No | No |
| Desch, 1993 | No | No | No | No |
| Hillner, 1993 | No | No | No | No |
| Hillner, 1993 | No | No | No | No |
| Hillner, 1992 | No | No | No | No |
| Hillner, 1992 | No | No | No | No |
| Hillner, 1991 | No | No | No | No |
| Skedgel, 2009 | Yes/No | Yes | Yes | No |
| Vlaenderen, 2009 | No | Yes | Yes | No |
| Kurian, 2007 | No | Yes | No | Yes/No |
| Liberato, 2007 | No | Yes | No | Yes/No |
| Garrison, 2007 | No | Yes | No | No |
| Millar, 2007 | No | No | Yes | No |
| Skedgel, 2013 | Yes/No | No | Yes | Yes/No |
| Hedden, 2012 | No | Yes | Yes | No |

**Appendix 12. Model types, and transition states reported in the 29 included economic studies comparing different treatment strategies for treating women with primary breast cancer**

| Types of strategies | Author, year | Type of model | Disease state | Model disease and treatment related assumption | Rational for assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | |
| Surgery + RTx vs. surgery | Bai, 2012 | Markov model | RF, LR, DR, death from non-BC, death from BC | Duration of RTx benefit was for life time<br>The impact of the adverse effects on the costs and/or utilities was not considered | No |
| Surgery + RTx vs. surgery | Hayman,1998 | Markov model | DF, LR, DR, death from BC, death from non-BC | Patients with DR state can come back to remission state<br>The impact of the adverse effects on the costs and/or utilities was considered | No |
| Surgery + CTx vs. surgery | Hillner,1993 (a) | Markov model | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Omitting contralateral tumour<br>Patients cannot come back to 'recurrence free-state' after recurrence<br>Duration of CTx benefit lasted for 5 years<br>Toxicity occurred during the 1st year of treatment<br>Patients with CTx toxicities could come back to disease-free state (toxicity is reversible) | No |
| Surgery + CTx vs. surgery | Hillner, 1993 (b) | Markov model | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Omitting contralateral tumour<br>Duration of CTx benefit lasted for 5 years<br>Patients cannot come back to 'recurrence-free state' after recurrence<br>Toxicity occurred during the 1st year of Tx<br>Patients with CTx toxicities could come back to DF state (toxicity is reversible) | No |
| Surgery + CTx vs. surgery | Hillner, 1992 (a) | Markov model | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Omitting contralateral tumour<br>Patients with CTx toxicities could come back to DF state (toxicity is reversible)<br>Duration of CTx benefit lasted for 5 years<br>Toxicity occurred during the 1st year of treatment<br>Patients could not come back to 'recurrence-free state' after recurrence | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | |
| Surgery + CTx vs. surgery | Hillner,1992 (b) | Markov model | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Omitting contralateral tumour<br>Duration of CTx benefit lasted for 5 years<br>Patients with CTx toxicities could come back to disease-free state (toxicity is reversible)<br>Patients could not come back to 'recurrence-free state' after recurrence<br>Toxicity occurred during the 1st year of treatment | No |
| Surgery + CTx vs. surgery | Hillner, 1991 | Markov model | RF, minor CTx toxicities, major CTx toxicity, first recurrence, post first recurrence, second recurrence, post second recurrence, third recurrence, death | Omitting contralateral tumour<br>Duration of CTx benefit lasted for 5 years<br>Patients cannot come back to 'recurrence-free state' after recurrence<br>Patients with CTx toxicities could come back to disease- free state (toxicity is reversible)<br>Toxicity occurred during the 1st year of treatment | No |
| Surgery + CTx vs. surgery | Campbell, 2011 | Markov model | DF, LR, DR, contralateral tumour, death (BC or non-BC) | Duration of CTx benefit lasted for 10 years | No |
| Surgery + ETx vs. surgery | Yang, 2010 | Not stated | RF, LRR, DR, contralateral tumour, death | The impact of the adverse effects on the costs and/or utilities was considered | No |
| **Surgery + CTx+Trz vs. surgery + CTx** | | | | | |
| Surgery + CTx +Trz vs. surgery + CTx | Shiroiwa, 2008 | Markov model | RF, LR, DR, death (they also include more health states, but they didn't mention a lot about them) | Duration of Trz benefit lasted for 5 years, after that the risk of recurrence was the same as with non-Trz arm<br>Trz cardiotoxicity was reversible, and did not affect mortality<br>The impact of the adverse effects on the costs and/or utilities was considered | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery + CTx + Trz vs. surgery + CTx** | | | | | |
| Surgery + CTx+Trz vs. surgery + CTx | Kurian, 2007 | Markov model | RF, recurrence (didn't define any type of recurrence), CAT, CAT and recurrence, and death (any cause) | Duration of Trz benefit lasted for 4 years<br>Trz cardiotoxicity was reversible, and did not affect mortality | No |
| Surgery + CTx+Trz vs. surgery + CTx | Skedgel, 2009 | Markov model | DF +/- cardiotoxicity, LR (LR or RR or contralateral tumour) +/- cardiotoxicity, well after LR+/- cardiotoxicity, DR +/- cardiotoxicity, death | Second or third LR were DR<br>Risk of recurrence decreased over time and there was no more DR after 20 years<br>Duration of Trz benefit lasted for 5 years, after that the risk of recurrence was the same as with non-Trz arm<br>Trz cardiotoxicity was reversible, and did not affect mortality | No |
| Surgery + CTx+Trz vs. surgery + CTx | Dedes, 2007 | Markov model | DF, RR, LR, DR, death | Omitting contralateral tumour<br>Duration of Trz benefit lasted for 5 years, after that the risk of recurrence was the same as with non-Trz arm<br>Trz cardiotoxicity was reversible, and did not affect mortality<br>Toxicity occurred during the 1st year of treatment | No |
| Surgery+ CTx+Trz vs. surgery + CTx | Buendia, 2013 | Markov model | DF, LR (LRR and contralateral tumour), DR, CAT, death from MBC, death from non-BC | Second or third LR were DR<br>Patients with metastasis get treated with Trz<br>Duration of Trz benefit lasted for 5 years after that the risk of recurrence was the same as with non-Trz arm<br>Trz cardiotoxicity was reversible and did not affect mortality<br>Toxicity occurred during the 1st year of treatment | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery+CTx+Trz vs. surgery+CTx** | | | | | |
| Surgery+ CTx+Trz vs. surgery + CTx | Chen, 2009 | Markov model | DF, recurrence (LR and contralateral tumour), DR, CAT, death | Second or third LR were DR<br>Duration of Trz benefit lasted for 5 years after that the risk of recurrence was the same as with non-Trz arm | No |
| Surgery+ CTx+Trz vs. surgery + CTx | Hedden, 2012 | Markov model | Adj Trz, adj symptomatic CHF, adj CTx, RF, LR, nonprogressive metastatic, metastatic symptomatic CHF, progressive metastatic, nonprogressive metastatic (no Trz), death | The impact of the adverse effects on the costs and/or utilities was considered | No |
| Surgery+ CTx+Trz vs. surgery + CTx | Purmonen, 2011 | Markov model | No disease progression, distant progression, and death | Omitting LR<br>Risk of recurrence decreased over time and there was no more DR after 20 years<br>Patients with metastasis get treated with Trz<br>The impact of the adverse effects on the costs and/or utilities was not considered<br>Duration of Trz benefit lasted for 5 years after that the risk of recurrence was the same as with non-Trz arm | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years**<br>**Surgery+CTx+Trz vs. surgery+CTx** | | | | | |
| Surgery+ CTx+Trz vs. surgery + CTx | Norum, 2007 | Not stated | Adj CTx/RTx Trz, follow up, heart failure, RF, DR, Paclitaxel/Tratuzumab, Vinorelbine, treatment of relapse, and death | Not stated | No |
| Surgery+ CTx+Trz vs. surgery + CTx | Hall, 2011 | Markov model | DF, symptomatic or asymptomatic CAT, recurrence (LRR or DR or contralateral tumour +/- CAT, DF after LR +/- CAT, and death | Second or third LR were DR<br>The impact of the adverse effects on the costs and/or utilities was considered<br>Trz cardiotoxicity was reversible, and did not affect mortality<br>Toxicity occurred during the 1st year of treatment | Yes |
| Surgery+ CTx+Trz vs. surgery + CTx | Liberato, 2007 | Markov model | DF, LR, DF after LR, DR, and death | Patients could not come back to 'recurrence free-state' after recurrence<br>Duration of Trz benefit lasted for 5 years after that the risk of recurrence was the same as with non-Trz arm<br>Trz cardiotoxicity was reversible and did not affect mortality | No |
| Surgery+ CTx+Trz vs. surgery + CTx | Garrison, 2007 | Markov model | Treatment, DF, DR, and death | Omitting LR<br>Omitting contralateral tumour<br>Trz cardiotoxicity was reversible and did not affect mortality | Yes |
| Surgery+ CTx+Trz vs. surgery + CTx | Millar, 2007 | Markov model | DF, LR or RR, DR, death from MBC, and non BC | Second or third LR were DR<br>Omitting contralateral tumour<br>The impact of the adverse effects on the costs and/or utilities was considered<br>Trz cardiotoxicity was reversible and did not affect mortality | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery +ETx+CTx vs. surgery+ETx or CTx** | | | | | |
| Surgery+ ETx+ CTx vs. surgery+ ETx | Karnon, 2002 | DES | DF, LR or RR, DFS after LR or RR, DR, death | Second or third LR were DR<br>The impact of the adverse effects on the costs and/or utilities was considered | No |
| **Age >65 years** | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | |
| Surgery+ CTx vs. surgery | Desch,1993 | Markov model | Complete response, CTx with minor toxicity, CTx with major toxicity, first recurrence, death | Natural history of the disease in younger patients was similar to the elderly<br>Patients did not have any co-morbidities<br>Patients could not come back to 'recurrence-free state' after recurrence<br>Duration of CTx benefit lasted for 5 years<br>Toxicity occurred during the 1st year of treatment | No |
| **Surgery +ETx+CTx vs. surgery+ETx or CTx** | | | | | |
| Surgery+ ETx+ CTx vs. surgery+ CTx | Naeim, 2005 (a) | Not stated | Not stated | Not stated | No |
| Surgery+ ETx+ CTx vs. surgery+ ETx vs. surgery+CTx | Naeim, 2005 (b) | Not stated | Not stated | Not stated | No |
| **Surgery+CTx+Trz vs. surgery+CTx** | | | | | |
| Surgery+ CTx+Trz vs. surgery + CTx | Vlaenderen, 2009 | Markov model | DF, local recurrence, DR, CAT, and death<br>Temporary state: LR or RR, MR, and DFS during the first 5 years after treatment | Not stated | No |

**(Continue Appendix 12.)**

| Types of strategies | Author, year | Type of model | Disease states | Model disease and treatment related assumption | Rationale for the assumption |
|---|---|---|---|---|---|
| **Age 50-65 years** | | | | | |
| **Surgery+CTx+Trz vs. surgery+CTx** | | | | | |
| Surgery+ CTx+Trz vs. surgery + CTx vs. surgery | Skedgel, 2013 | Markov model | DF +/- cardiotoxicity, LR (LR or RR or contralateral tumour) +/- cardiotoxicity, RFS after LR+/- cardiotoxicity, DR +/- cardiotoxicity, death | Omitting contralateral tumour<br>Second or third LR were DR<br>Risk of recurrence decreased over time and there was no more DR after 20 years<br>Trz cardiotoxicity was reversible, and did not affect mortality<br>Duration of Trz benefit lasted for 5 years after that the risk of recurrence was the same with non-Trz arm | No |
| **Age group not mentioned** | | | | | |
| Surgery+ RTx vs. surgery | Lievens, 2005 | Markov model | RF, LR or RR or DR, death of BC, and death of non-BC | The impact of the adverse effects on the costs and/or utilities was considered | No |

**(Note)** DF: disease free; RF: relapse free; LR: local recurrence, DR: distant recurrence; LRR: locoregional recurrence ; Adj: adjuvant; CTx: chemotherapy; RTx: radiotherapy; RR: regional recurrence; Trz: trastuzumab; CAT: cardiotoxicity ; MBC: metastatic breast cancer; BC: breast cancer; CHF: congestive heart failure.

**Appendix 13. Costs, outcomes, and incremental benefit/cost results reported in the 29 included economic studies comparing different treatment strategies for treating women with primary breast cancer**

| Age | Type of strategies | Author | Type of model | Benefit results | Cost results | Benefits/costs combination results |
|---|---|---|---|---|---|---|
| **Age >65 years old** | | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | | |
| | Surgery + CTx vs. surgery | Desch, CE | Markov model | 2.8 QALYs<br>2.8 QALYs<br>2.2 QALYs<br>1.8 QALYs<br>1.4 QALYs | Not stated | $28,200/ QALY (60yrs)<br>$31,300/ QALY (65yrs)<br>$36,300/ QALY (70yrs)<br>$44,400/ QALY (75yrs)<br>$57,100/ QALY (80yrs)<br>$14,910/ LYG (60yrs)<br>$24,400/ LYG (75yrs) |
| | Surgery + ETx vs. surgery | Yang, JJ | Not stated | Not stated | $16,311 vs. 13,064 (ER+/PR+, LN+)<br>$15,810 vs. 10,488 (ER+/PR+, LN-)<br>$15,570 vs. 11,535 (ER+/PR+,<39yrs)<br>$16,274 vs. 12,169 (ER+/PR+, 40-49yrs)<br>$15,337 vs. 11,341 (ER+/PR+, >50yrs)<br>$14,777 vs. 13,663 (ER+/PR- or ER-/PR+, LN+)<br>$15,217 vs. 11,241 (ER+/PR- or ER-/PR+, LN-)<br>$14,926 vs. 11,986 (ER+/PR- or ER-/PR+,<39yrs)<br>$14,761 vs. 12,819 (ER+/PR- or ER-/PR+, 40-49yrs)<br>$14,573 vs. 11,631 (ER+/PR- or ER-/PR+, >50yrs) | $1939/ LYG (ER+/PR+, LN+)<br>$1203/ LYG (ER+/PR+, LN-)<br>$1137/ LYG (ER+/PR+, <39yrs)<br>$1895/ LYG (ER+/PR+, 40-49yrs)<br>$739/ LYG (ER+/PR+, >50yrs)<br>$1337/ LYG (ER+/PR- or ER-/PR+, LN+)<br>$1383/ LYG (ER+/PR- or ER-/PR+, LN-)<br>$1949/ LYG (ER+/PR- or ER-/PR+, <39yrs)<br>$3107/ LYG (ER+/PR- or ER-/PR+, 40-49 yrs)<br>$1217/ LYG (ER+/PR- or ER-/PR+, >50yrs) |

**(Continue Appendix 13.)**

| Age | Type of strategies | Author | Type of model | Benefit results | Cost results | Benefits/costs combination results |
|---|---|---|---|---|---|---|
| **Age >65 years old** | | | | | | |
| | Surgery + CTx+Trz vs. surgery + CTx | Liberato, NL | Markov model | 9.22 QALY vs. 8.03 QALY<br>9.82 LYG vs. 8.80 LYG | Italy: €54,058 vs. €36,522<br>US:$77,947 vs. $55,562 | 50 years<br>Italy: €17,192 / LYG (6,911, 47,179), €14,861/ QALY (3,917, 44,028)<br>US: $2,946/ LYG (7,061, 55,168), $18,970/ QALY (6,014, 45,621)<br>Over 75 years<br>>€50,000/ QALY ($60,000/QALY)<br>Over 79 years<br>>€100,000/ QALY($150,000/ QALY) |
| | Surgery + CTx+Trz vs. surgery + CTx | Millar, JA | Markov model | Not stated | | 50 years<br>52 weeks of Trz: $22,793/ QALY, $13,730/ LYG<br>9 weeks of Trz: $1700/ QALY, $1016/ LYG<br>Over 65 years<br>$27,734/ QALY |
| | Surgery + CTx+Trz vs. surgery + CTx vs. surgery | Skedgel, C | Markov model | Not stated | Not stated | Not stated |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Surgery + CTx + Trz vs. surgery + CTx | Vlaender en, IV | Markov model | Not stated | Not stated | €6,478/ QALY (3,704, 10,345) (<50yrs)<br>€8,131/ QALY (4,793, 13,436) (50-59yrs)<br>€11,868/ QALY (6,636, 20,224) (60-69yrs)<br>€25,755/ QALY (13,708, 42,908) (70-79yrs)<br>€100,356/ QALY(53,944, 206,007) (>80yrs)<br>Weighted mean ICER: €10,163/ QALY |

**(Continue Appendix 13.)**

| Age | Type of strategies | Author | Type of model | Benefit results | Cost results | Benefits/costs combination results |
|---|---|---|---|---|---|---|
| **Age >65 years old** | | | | | | |
| **Surgery +ETx + CTx vs. surgery+ETx or CTx** | | | | | | |
| | Surgery + ETx+ CTx vs. surgery + CTx | Naeim, A | Not stated | Not stated | CMF or AC vs. tam vs. tam-AC: 10,194$/ QALY vs. $22,220/ QALY [65yrs, node (-), ER (+)]<br>$4568 vs. $5965 vs. $6320 vs. $10,923 vs. $12,320 | Tam vs. CMF or AC: $10,19/ QALY<br>Tam-AC vs. Tam: $22,22/ QALY [65yrs, node (-), ER (+)]<br>CMF vs. no Adj: $30,45/ QALY<br>AC vs. CMF: $46,57/ QALY [65yrs, node (-), ER (-)]<br>Tam vs. no Adj : $19,53/ QALY<br>Tam-AC vs. Tam: $54,53/ QALY (assume efficacy not decline with age)<br>Tam-AC vs. Tam: $280,00/ QALY (assume efficacy decline with age) [75yrs, node (-), ER (+)]<br>AC vs. no Adj : $75,56/ QALY [75yrs, node (-), ER (-)] |

**(Continue Appendix 13.)**

| Age | Type of strategies | Author | Type of model | Benefit results | Cost results | Benefits/costs combination results |
|---|---|---|---|---|---|---|
| **Age >65 years old** | | | | | | |
| | Surgery + ETx+ CTx vs. surgery + ETx vs. surgery + CTx | Naeim, A | Not stated | Not stated | $4568 vs. $5965 vs. $6320 vs. $10,923 vs. $12,320 | Tam vs. CMF or AC: $6,52/ QALY<br>Tam-CMF vs. Tam: $12,89/ QALY<br>Tam-AC vs. Tam-CMF: $13,97/ QALY [65 node (+), ER(+)] AC vs. no Adj : $22,94/ QALY [65yrs, node (+), ER (-)]<br>Tam vs. no Adj: $10,97/ QALY<br>Tam-AC vs. Tam: $27,41/ QALY<br>Tam-AC vs. Tam: $120,00/ QALY(assume efficacy decline with age) [75yrs, node (+), ER (+)]<br>AC vs. no Adj: $42,61/ QALY [75yrs, node (+), ER (-)]<br>Tam vs. no Adj: $26,46/ QALY [85yrs, node (+), ER (+)] |
| **Age 50-65 years old** | | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | | |
| | Surgery+ CTx vs. surgery | Hillner, BE | Markov model | Not stated | Not stated | $18,80/ QALY |
| | Surgery+ CTx vs. surgery | Hillner, BE | Markov model | Not stated | Not stated | 60 yrs old: $28,20/ QALY<br>75 yrs old: $44,40/ QALY |
| | Surgery+ CTx vs. surgery | Hillner, BE | Markov model | Not stated | Not stated | $18,800/ QALY |
| | Surgery+ CTx vs. surgery | Hillner, BE | Markov model | Not stated | Not stated | $18,800/ QALY |

**(Continue Appendix 13.)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Age 50-65 years old** | | | | | | |
| **Surgery plus Adj therapy vs. surgery** | | | | | | |
| | Surgery+ CTx vs. surgery | Hillner, BE | Markov model | Not stated | Not stated | 18,800$/ QALY |
| | Surgery+ CTx vs. surgery<br>Surgey + CTx vs. surgery + CTx | Campbell, HE | Markov model | 10.93 QALY vs. 12.35 QALY vs.12.66 QALY vs.12.88 QALY | £10.93 vs. £12.35 vs. £12.66 vs. £12.88 | Dom vs. £603/ QALY vs. £13,704/ QALY |
| | Surgery + RTx vs. surgery | Bai, Y | Markov model | 13.25 QALY vs. 11.75 QALY (overall)<br>13.79 QALY vs. 12.19 QALY (Node -)<br>9.75 QALY vs. 8.44 QALY (node +)<br>22,20 LYG vs. 19,51 LYG (overall)<br>23.22 LYG vs. 20.30 LYG (node-)<br>15.89 LYG vs. 13.64 LYG (node+) | $24,518.9 vs. $25,147.0 (overall)<br>$22,744.0 vs. $23,668.7 (node -)<br>$34,874.7 vs. $35,305.2 (node+) | $-420,56/ QALY (overall)<br>$-576.53/ QALY (node -)<br>$-328.18/ QALY (node +)<br>$-233.20/ LYG (overall)<br>$-316.14/ LYG (node -)<br>$-191.11/ LYG (node +) |
| | Surgery+ RTx vs. surgery | Hayman, JA | Markov model | 7.19 QALY vs. 6.84 QALY | $27,200 vs. $17,400 | $28,00/ QALY |
| **Surgery+CTx+Trz vs. surgery+CTx** | | | | | | |
| | Surgery+ CTx+Trz vs. surgery + CTx | Buendia, JA | Markov model | 7.62 QALY vs. 6.83 QALY<br>9.35 LYG vs. 8.53 LYG | $132,361 vs $75,315 | $71,94/ QALY<br>$69,70/ LYG |
| | Surgery+ CTx+Trz vs. surgery + CTx | Hall, PS | Markov model | 7.714 QALY vs. 7.225 QALY | £40,622 vs. £27,993 | £25,803/ QALY |
| | Surgery+ CTx+Trz vs. surgery + CTx | Chen, W | Markov model | 14.28 QALY vs. 11.45 QALY<br>18.17 LYG vs. 15.30 LYG | $83,967 to 86,276 vs. $61,210 to $63,529 | $7564 to $7933/ LYG<br>$7676 to $8049/ QALY |
| | Surgery+ CTx+Trz vs. surgery + CTx | Purmonen, TT | Markov model | 8.37 QALY vs. 7.71 QALY | €61,600 vs. €53,700 | €12,00/ QALY |
| | Surgery+ CTx+Trz vs. surgery + CTx | Dedes, KJ | Markov model | Not stated | €67,682 vs. €47,791 | €19,67/ LYG |

| | | | | | |
|---|---|---|---|---|---|
| Surgery+ CTx+Trz vs. surgery + CTx | Shiroiwa , T | Markov model | Not stated | Not stated | €18,00/ LYG |

**(Continue Appendix 13.)**

| | | | | | |
|---|---|---|---|---|---|
| **Age 50-65 years old** | | | | | |
| **Surgery+CTx+Trz vs. surgery+CTx** | | | | | |
| Surgery+ CTx+Trz vs. surgery + CTx | Norum, J | Not stated | Not stated | Not stated | €15, 34/ LYG (20% improvement in OS)<br>€35,94/ LYG (10% improvement in OS)<br>€19,17/ QALY (20% improvement in OS)<br>€44,934/ QALY (10% improvement in OS) |
| Surgery+ CTx+Trz vs. surgery + CTx | Skedgel, C | Markov model | Not stated | Not stated | 5-year benefit: $70,292/ QALY (28,602, 139,657)<br>3-year benefit: $127,862/ QALY (56,912, 247,926) |
| Surgery+ CTx+Trz vs. surgery + CTx | Kurian, AW | Markov model | Base case: 10.77 QALY vs. 9.35 QALY<br>PSA: 10.79 (10.08-11.61) vs. 9.40 (8.55 to 10.26)<br>Base case: 14.01 LYG vs. 12.29 LYG | Base case: $190,092 vs. $133,429<br>PSA: $189,988 ($185,988 to $193,565) vs. $133,204 ($129,236 to $137,078) | Base case: $39,892/ QALY<br>PSA case: $56,491/ QALY ($18,727 to $168,787)<br>Base case: $32,816/ LYG |
| Surgery+ CTx+Trz vs. surgery + CTx | Garrison Jr | Markov model | Societal perspective: 11.78 QALY vs. 10.08 QALY<br>Payer perspective: 11.78 QALY vs. 10.08 QALY<br>Societal perspective: 13.72 LYG vs. 11.88 LYG<br>Payer perspective: 13.72 LYG vs. 11.88 LYG | Societal perspective: $75,746 vs. $28,749<br>Payer perspective: $73,672 vs. $28,749 | Societal perspective: $27,637/ QALY<br>$25,542/ LYG<br>Payer perspective: $26,417/ QALY<br>$24,435,417/ LYG |
| Surgery+ CTx+Trz vs. surgery + CTx | Hedden, L | Markov model | Not stated | Not stated | $13,095/ QALY<br>$15,492/ LYG |

**(Continue Appendix 13.)**

| | | | | | |
|---|---|---|---|---|---|
| **Age 50-65 years old** | | | | | |
| **Surgery +ETx+CTx vs. surgery+ETx or CTx** | | | | | |
| Surgery+ ETx+ CTx vs. surgery+ ETx | Karnon, J | DES | 12.14 QALY vs. 11.56 QALY | £9146 vs. £7115 | £3483/ QALY |
| **Not mentioned** | | | | | |
| Surgery+ RTx vs. surgery | Lievens, Y | Markov model | 7.104 QALY vs. 6.877 QALY<br>9.367 LYG vs. 9.132 LYG | €20 vs. €30 | €43,860/ QALY<br>€42,553/ LYG |

**(Note)** QALY: quality adjusted life year; LYG: life year gained; ETx: endocrine therapy; CTx: chemotherapy; DES: discrete event simulation; OS: overall survival; PR: progesterone receptor; ER: oestrogen receptor; RTx: radiotherapy; LN: lymph node; Tam: tamoxifen; CMF: cyclophosphamide, methotrexate, fluorouracil; US: united states; PSA: probabilistic sensitivity analysis