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Holmes, G.R. orcid.org/0000-0002-8861-9638, Ward, S.E., Brennan, A. orcid.org/0000-0002-1025-312X et al. (27 more authors) (2021) Cost-effectiveness modeling of surgery plus adjuvant endocrine therapy versus primary endocrine therapy alone in UK women aged 70 and over with early breast cancer. Value in Health, 24 (6). pp. 770-779. ISSN 1098-3015

https://doi.org/10.1016/j.jval.2020.12.016

Cost effectiveness modelling of surgery plus adjuvant endocrine therapy versus primary endocrine therapy alone in UK women aged 70 and over with early breast cancer

Abstract

Objectives: Approximately 20% of UK women aged 70+ with early breast cancer receive primary endocrine therapy (PET) instead of surgery. PET reduces surgical morbidity but with some survival decrement. To complement and utilise a treatment dependent prognostic model, we investigated the cost-effectiveness of surgery plus adjuvant therapies versus PET for women with varying health and fitness, identifying subgroups for which each treatment is cost-effective.

Methods: Survival outcomes from a statistical model, and published data on recurrence, were combined with data from a large, multicentre, prospective cohort study of over 3400 UK women aged 70+ with early breast cancer and median 52 month follow up, to populate a probabilistic economic model. This model evaluated the cost effectiveness of surgery plus adjuvant therapies relative to PET for 24 illustrative subgroups: Age {70, 80, 90} x Nodal status {FALSE (F), TRUE (T)} x Comorbidity score {0,1,2,3+}.

Results: For a 70 year old with no lymph node involvement and no comorbidities (70,F,0), surgery plus adjuvant therapies was cheaper and more effective than PET. For other subgroups, surgery plus adjuvant therapies was more effective but more expensive. Surgery plus adjuvant therapies was not cost-effective for 4 of the 24 subgroups: (90,F,2), (90,F,3), (90,T,2), (90,T,3).

Conclusion: From a UK perspective, surgery plus adjuvant therapies is clinically effective and cost effective for most women aged 70+ with early breast cancer. Cost effectiveness reduces with age and comorbidities and for women over 90 with multiple comorbidities, there is little cost benefit and a negative impact on quality-of-life.

Introduction

Breast cancer is a common cancer in older women with one third of all cases occurring in women aged 70+(1). Older age is associated with rising rates of comorbidity and frailty and with reduced life expectancy. As a consequence, the impact of breast cancer on mortality is relatively less in this age group(2) and there are concerns about the risk of over-treatment(3) and reduced treatment tolerance(3). As a further consequence of this, rates of use of standard treatments for breast cancer are lower in older women(4, 5). Surgery plus adjuvant therapies is standard of care. Primary endocrine therapy (PET) is the sole use of antioestrogen tablets, omitting surgery and other adjuvant therapies altogether(6). PET results in shrinkage or even complete disappearance of the breast cancer over the course of the first year of therapy. However, about 10% of cases do not respond (primary resistance) and about 40% will start to regrow after a few years, requiring a change of management(7). In place of standard of care, PET is widely used in the management of frail or comorbid older women where the morbidity risks of surgery are higher and life expectancy is likely to be relatively short (not more than around 5 years). Furthermore, chemotherapy is seldom given to women over the age of 80, even when risk of recurrence is high(4), and radiotherapy is often omitted following breast conservation surgery(BCS)(8).

Omission of standard therapies in older women with breast cancer have included omission of radiotherapy after breast conservation, of which the best example is the PRIME II trial(9) but the CALGB 9343(10) and BASO II(11) trials also gave similar findings, namely that in older women with ER+ low risk breast cancer radiotherapy may safely be omitted after breast conservation surgery. There is also evidence that omission of chemotherapy in older women with high recurrence risk breast cancer may be safe in some breast cancer subtypes (namely ER+ breast cancer), although this is not based on specific randomised trial data but rather on observational data(12). There are no data, however, relating to personalised tailoring of treatment based on the health and fitness of the patient. Data to guide such precision medicine is also currently lacking in National(13) and International (14) guidelines. Several randomised trials were conducted over 20 years ago which individually, and on meta-analysis, showed no significant difference in survival outcomes between PET and surgery plus adjuvant therapies at 5 year follow up, although a subsequent patient-level

meta-analysis with longer-term follow up has shown that survival is enhanced in women who have surgery(15). The randomised trials had limitations (16). The median age of the recruited women was 76, an age at which PET would rarely be offered under current practice. The trials used tamoxifen as the antioestrogen, whereas modern practice would be to offer letrozole, an aromatase inhibitor, which has greater efficacy(16). Importantly, they recruited women without specifying that tumours must be ER positive, so up to 20% of cases in the PET group will have effectively been treated with placebo tablets. It is likely that selecting women with strongly ER-positive cancers and who are older, frailer and more co-morbid, would identify a subgroup of women for whom use of PET is to be preferred, with minimal risk of increased mortality, together with reduced morbidity and enhanced quality-of-life.

The Age Gap prospective observational cohort study was a UK study, which set out to identify the threshold for use of PET in older women (17, 18). It recruited 3,414 women aged 70+ (median age 83, range 79-88, for women treated with PET) with operable breast cancer. The study collected detailed baseline data about tumour stage, grade, biotype and nodal involvement alongside detailed health and fitness data using a range of validated scoring systems such as the Charlson comorbidity score(19) and the Activities of Daily Living score (ADL)(20).

A systematic literature review in 2014(21) and subsequent updated searches showed that cost effectiveness modelling comparisons between surgery with adjuvant endocrine therapy and PET alone have not been previously undertaken. In response to this gap in the research, the evidence which has emerged from the AGE-GAP project was combined with other evidence in a de-novo cost effectiveness model comparing the two treatment strategies. The analysis estimated the life expectancy and quality adjusted life years (QALYs) for each strategy, using payer perspective lifetime discounted NHS costs and social care costs. The model was applied to 24 illustrative subgroups of patients in order to determine for which patients PET is more cost-effective than surgery plus adjuvant therapies. These subgroups were defined by all combinations of the following patient characteristics: age at diagnosis (70, 80, 90), nodal involvement (FALSE, TRUE) and comorbidity score (0,1,2,3+, being Charlson score(19) minus age component). For each subgroup, we estimated the incremental cost effectiveness ratio i.e. incremental cost per QALY gained by surgery plus adjuvant endocrine

therapy versus PET alone. We also estimated the uncertainty associated with these estimates via probabilistic sensitivity analysis (PSA).

Methods

A probabilistic model was developed in the open source software package R version 3.4.1(22). A partitioned survival model (PSM) area under curve (AUC) approach was selected because the output of the statistical prognostic model (introduced above) was overall survival. The model had three health states: disease free after primary treatment, disease free after treatment for loco-regional relapse in the Surgery arm (i.e. the tumour has returned) or progression in the PET arm (i.e. the tumour has continued to grow) and dead. It was assumed that a maximum of one loco-regional relapse or progression could occur. The cost and impact on quality of life associated with metastatic disease was incorporated as a one off cost and utility decrement at the time of death. This was based on the assumption that only patients with metastatic disease would die of breast cancer. Due to lack of more detailed appropriate evidence, a single average length of time with metastatic disease, for both treatments and all subgroups, was derived from the exponential death rate reported by Chang et al(23), where estimates were reported for the 50+ age group.

The overall survival curves and cause of death, for the PET and surgery arms, were modelled using a model previously developed for prediction of outcomes to support the online Age Gap Decision Tool for the PET versus Surgery plus adjuvant therapies decision as described in the introduction(24). Briefly, patient data for women aged 70+ with a first diagnosis of invasive breast cancer between 2002 and 2010 were obtained from the West Midlands and the Northern and Yorkshire cancer regions. Associated survival data were provided by Public Health England with a censoring date of the 17th January 2017. After pre-processing and exclusions, the data for 18,727 individuals, with a median follow up of 8.3 years, were used for model training. Hazard of breast cancer mortality (BCM) was modelled using a Royston-Parmar restricted cubic spline model(25) and other cause mortality (OCM) using a proportional hazards models. The outputs of the BCM and OCM models were combined according to competing hazards rules to produce overall survival curves and the associated proportions of BCM and OCM deaths. This resulted in a combined model with eight variables as inputs: patient age, comorbidity score, and ADL score; tumour grade and size; lymph node status;

and treatment received (surgery plus adjuvant therapies or PET). To inform the cost-effectiveness analysis for a particular subgroup, the combined statistical model was used to produce overall survival curves and proportions of BCM / OCM deaths for each treatment and for each possible value of ADL score, tumour grade and for tumour sizes 5, 15, 35 and 60 mm. A single survival curve for each treatment and subgroup was produce by weighted averaging over the combinations of ADL, grade and tumour size using appropriate weights derived from the joint distribution of these variables in the Age Gap cohort data(18).

Recurrence data was not available from the registry data. The baseline progression free survival (PFS) curve (i.e. that following surgery) was therefore modelled using a 2-piece constant hazard with the cut point at 24 months, with adjustment for age and nodal status, and with parameters derived from the ATAC trial(26). The justification for using these data sources is that it provided data on medium to long-term risk of recurrence for a population of appropriate age profile (75 and over) who were treated with surgery and adjuvant endocrine therapy, taken from a high-quality study. The method of Guyot et al(27) was used to recreate individual patient survival data (IPD) from the published Kaplan-Meyer (KM) curves. Further details of the baseline PFS derivation are in Section 1 of Supplementary materials. A hazard ratio, applied to the baseline PFS curve to create a curve for the PET arm, was taken from Morgan et al(16). This hazard ratio was derived from the GRETA trial(28) which was judged to be the only trial reporting evidence for this outcome relevant to the 70+ age group. Our model relies on the assumption that these data sources are compatible.

The resource use inputs include endocrine therapy, surgery, hospitalisations, outpatient appointments and costs of recurrence and metastatic disease. Complete tables of the parameters used in the model are set out in Table 1, Table 2 and Table 3. Also shown are the standard error and distribution for each parameter where appropriate which were used for the sensitivity analyses. Short-term resource use was taken from the Age Gap cohort study, where feasible. Where Age Gap data was not available, standard approaches were used to incorporate evidence using routine sources including published literature.

Rates of mastectomy, breast conserving surgery (BCS), sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) were age dependent(16, 29). Patients receiving PET were assumed not to receive chemotherapy but for surgery patients an average risk of death during chemotherapy was applied(30). The proportion of patients receiving radiotherapy was averaged over the types of primary surgery received. For the surgery arm, a distribution for lymphoedema status and severity was specified(31). This was also related to the probability of a patient having axillary lymph node dissection (ALND).

Treatment costs are shown in Table 2. Costs were taken from the NHS reference costs and the British National Formulary (BNF)(32), or the wider literature, as appropriate. Costs were inflated to 2016-17 levels, where necessary, using unit costs from the Personal Social Services Research Unit. The cost of surgery is age dependent (due to the proportions having different procedures also varying by age) and comorbidity score dependent (as the level of comorbidity impacts on the rate of surgical complications). The average surgery costs also took into account the proportions of patients taking different pathways through SNLB, ALND, and positive margin re-excision.

For chemotherapy costs, a weighted average of four commonly used regimens was used informed by expert opinion. An average toxicity cost was added and the total average cost was applied to the surgery arm. Endocrine therapy was assumed to have been taken daily for each month survived, for 5 years (Surgery patients) or the rest of the patient's life (PET patients). The cost of endocrine therapy, ET, is averaged over a proportion of patients getting each of anastrozole, letrozole and exemestane and tamoxifen for simplicity although it is known that the majority of post-menopausal women receive aromatase inhibitors and in the adjuvant setting this is most usually anastrozole, whereas in the PET setting this is most often letrozole.
The average cost of lymphoedema, taking into account incidence and severity rates by age, was added to the surgery arm. Average osteoporosis rates(33) were used to apply costs of bisphosphonates, taken from the BNF.

Follow up for surgery plus adjuvant therapies patients assumed that they received a 6 monthly appointment with a clinician for 2 years, then yearly for a further 3 years, with 1 mammogram per

year. For PET patients follow up with clinician and ultrasound was assumed to be 3 monthly for 1 year, then 6 monthly for the next 4 years, although we are aware that use of ultrasound for follow up is variable between units and patients. Cost of mammograms and outpatient follow-up appointments were taken from NHS reference costs. Cost of diagnosis was taken from Hind et al(34).

Treatment costs after loco-regional relapse or progression were dependent on comorbidity score(35). An average chemotherapy cost post LRR was also applied to each patient. Follow-up costs post LRR were as for follow-up after primary treatment. In the surgery arm a LRR triggered a new 5 year schedule of follow up; the follow up remained unchanged in the PET arm. Patients who died of breast cancer were assumed to experience additional costs while living with metastatic disease and for palliative care over the last 3 months prior to death, based on Karnon et al (2007)(36) which were included in the one off cost at the time of BCM.

Health related utility was based on the EQ-5D. The EQ-5D is a standardised generic instrument which describes and values health-related quality of life and provides a single index value for use in economic evaluation. Utilities were drawn from the literature and based on Lidgren et al 2007(37). Utilities were adjusted for age(38), comorbidity(39) and lymphoedema(40). Short-term decrements after surgery (3 months)(41) and for patients receiving chemotherapy (12 months) were also applied.

Costs and benefits were calculated on a month-by-month basis and are discounted at a rate equivalent to 3.5% p.a. in line with the NICE reference case. The resulting incremental cost effectiveness ratio ICER was calculated for each patient subgroup. Deterministic sensitivity analysis was carried out to examine the impact on the results of changes in key input parameters, including the effectiveness of surgery plus adjuvant therapies versus PET, the cost of surgery, endocrine therapy and utility following surgery. In all 123 individual parameters or groups of parameters (e.g. all surgery costs) were varied to the lower and upper limits of the 95% confidence intervals.

Uncertainty in model outputs was evaluated using PSA, by jointly varying each parameter within its distribution to investigate the impact of parameter uncertainty on the results obtained. Probability

distributions were derived from the statistical analysis of the observational study and other evidence, where appropriate. Results of PSA were plotted on the cost-effectiveness plane.
In order to check the clinical outputs of the model, the total number of Progressions (PET), Recurrences (Surgery), Breast cancer mortalities (BCM) and Other cause mortalities (OCM) up to 2 and 5 years post-diagnosis, for the PET and Surgery treatment arms were extracted from the model output.

RESULTS

The base case incremental cost effectiveness results for surgery plus adjuvant therapies versus PET are presented in Table 4. Surgery plus adjuvant therapies was predicted to deliver higher QALYs than PET and was also cheaper for subgroup 1 (70, FALSE, 0), i.e. surgery plus adjuvant therapies dominated PET for this subgroup which represents the youngest, fittest patients considered. The ICER remained below £10,000 for the majority of subgroups and only increased above this for subgroups representing the oldest, least fit patients. Surgery plus adjuvant therapies was also predicted to be cost effective at a threshold of £20,000 for all patient groups except for patients age 90 with a comorbidity score of 2 or 3 regardless of nodal status (i.e. subgroups 19,20, 23 and 24 in Table 4).

Oneway sensitivity analysis results are shown in Figure 3 and Figure S4. Figure S4 shows that for the majority of subgroups (subgroups 1-18 & 21-22), the biggest variations were related to the mortality rate of patients with metastatic cancer. Other influential parameters were the cost of radiotherapy and the monthly costs of metastatic disease. However, in none of these cases was the ICER raised near to the £20,000 threshold being always less than £15,000. All other parameters caused less variation than the three shown for each subgroup. Figure 3 shows the five most influential parameters for the remaining four subgroups (subgroups 19,20,23,24 representing patients age 90 with 2+ comorbidities). These subgroups all had base case incremental QALYs of less than 0.16 and hence the ICERs were expected to be more sensitive to parameter changes. These were also the subgroups for which surgery plus adjuvant therapies was not found to be cost effective at the £20,000 threshold. The most influential parameters were mortality rate for patients with metastatic

disease, utility of patients with metastatic disease, utility 1+ years after treatment (with no further recurrence, progression) and radiotherapy cost. For subgroup 19 : (90, FALSE, 2), the base case ICER of £29,852 is reduced to £20,648 by the upper level of metastatic death rate, whilst the lower level of metastatic utility raised it to £37,223. For subgroup 20 : (90, FALSE, 3), the base case ICER of £69,124 was reduced to £47,029 by the lower limit of metastatic death rate. For subgroup 23 : (90, TRUE, 2), the base case ICER of £21,533 varied between £14,481 and £25,970 with metastatic death rate. For subgroup 24 : (90, TRUE, 3), the baseline ICER of £42,268 was reduced to £28,915 by the upper limit of metastatic death rate and increased to £56,239 by the lower limit of utility with metastatic disease. Thus the case for surgery plus adjuvant therapies not being cost effective is very strong and strong respectively for subgroups 20 and 24, but is less so for subgroups 19 and 23 and with more dependence on the chosen level of cost effectiveness threshold.

The PSA results for each subgroup are presented as cost effectiveness acceptability curves in Figure 2. This is complemented by the final column in Table 4, which shows the probability of surgery plus adjuvant therapies being cost-effective at the £20,000 threshold, for each subgroup. The probability of cost-effectiveness always decreased with age and with increasing comorbidity score. Nodal involvement also decreased the probability except in 90 year olds with comorbidities where it was either unchanged (comorbidity score of 1, i.e. comparing subgroups 18 & 22) or increased. Surgery plus adjuvant therapies had 94% chance of being cost-effective for subgroup 1 (70, FALSE, 0), and 24% for subgroup 23 (90, FALSE, 3).

A comparison between the base case incremental results and the mean of the PSA incremental analysis is shown in Table S1. There were relatively small differences in the ICERs using these 2 methods and no subgroups where a change in decision was indicated.

The clinical output results for each subgroup including number of recurrences, progressions, BCM and OCM predicted by the model are shown in Table S2. To take a single example, for subgroup 5 (70, TRUE, 0), after 5 years, for every 1,000 patients treated, 44 local recurrences and 109 breast cancer deaths were predicted after surgery plus adjuvant therapies compared to 62 local

progressions and 248 breast cancer deaths following PET. Table S3 shows a partial breakdown of the costs incurred by subgroups and treatments.

Discussion

This study found that surgery plus adjuvant therapies is likely to be the optimal breast cancer treatment for the majority of women aged 70 and over, both in terms of survival and cost-effectiveness, from a UK perspective. Among the 24 illustrative patient subgroups analysed, PET was predicted to be cost-effective only for 4, those representing women aged 90 with a comorbidity score of 2 or 3 regardless of nodal status. This cost effectiveness of surgery plus adjuvant therapies was largely driven by the significantly increased survival that is associated with surgery plus adjuvant therapies. In addition, the higher rate of local recurrence means that a significant number of PET patients subsequently undergo surgery. So despite the very low cost of endocrine therapy compared to surgery, the cost benefit of PET is overwhelmed by its lack of long term efficacy. Despite the fact that PET has a much lower short term impact on quality of life, in the longer term, the higher rate of recurrence, higher mortality and the need for subsequent surgery and other treatments outweighs this in all but the oldest and most co morbid groups.

Generally, the cost-effectiveness of surgery plus adjuvant therapies was found to decrease with increasing age and also decreased with increasing comorbidity score. For younger women, surgery plus adjuvant therapies was less cost effective when there was lymph node involvement, which may reflect the increased mortality due to metastatic disease in this group of women. For the oldest women considered, however, this situation was reversed and surgery plus adjuvant therapies was more cost-effective if there is lymph node involvement. This may reflect the fact that these women have more aggressive disease which may be less likely to respond to PET, although there is no way to confirm this hypothesis. The transition point for this was around the subgroups of 80 year old women with a comorbidity score of 2. With regard to the implications for clinical practice, these results suggest that for the majority of women over 70, surgery plus adjuvant therapies should be offered. Once a women reaches the age of 90, the cost effective benefit from surgery plus adjuvant therapies is much less and consideration should be given to PET if the patient wishes it.

This study has a number of limitations which should be considered when interpreting the results. Separate data sources were used to model the PFS curves and the OS curves. This was unavoidable due to the historic absence of good quality and consistent recurrence data in cancer registry data which was nevertheless needed to provide sufficient data, follow up and mortality events to adequately train the statistical survival model. Furthermore, a third data source was used to provide the hazard ratio for PFS. The rationale for these choices has been described in the methods section. It was judged that these were the best data sources currently available which were relevant and compatible with the treatment choice and patient age group being considered. A second limitation is the assumption that an individual can only have one local recurrence / progression event which is not the case in fact. Thirdly, it was assumed that patients die of breast cancer if, and only if, they have metastatic disease and that an average cost and utility decrement for this can be applied regardless of patient characteristics and treatment choice. It was judged that these latter two limitations were likely to have approximately equal effect on both treatment arms. Finally, it has already been noted that follow up procedures, and therefore associated costs, are likely to have quite wide local variation.

This study also has a number of strengths. The statistical OS model was trained and validated using large registry datasets which reflect treatment in a real world context and contain recent data with long term follow up. This model has been used to develop an online tool to support clinical decision between surgery plus adjuvant therapies or PET for older women. The tool has been validated(24) and is now MHRA approved. Importantly, our analysis examines cost effectiveness for subgroups of the older female patient population. A broader analysis would be likely to find surgery plus adjuvant therapies to be cost-effective but mask the fact that there are some groups of patients for whom this will not be the case. To the authors' knowledge, this is the first economic analysis of the PET versus surgery decision for this patient population and is therefore an important contribution to the literature and worthy of further research and development.

Conclusion

To investigate the cost-effectiveness of surgery plus adjuvant therapies versus PET for women age 70 and over with varying health and fitness, we constructed a novel probabilistic economic model and applied it to illustrative subgroups of patients differentiated by age, comorbidities and lymph node status. From a UK perspective, surgery plus adjuvant therapies is clinically effective and cost effective for the majority of women aged 70+ with early breast cancer. Cost effectiveness reduces progressively with age and comorbidities such that for women over 90 with multiple comorbidities, there is little cost benefit to be gained and a negative impact on quality-of-life.

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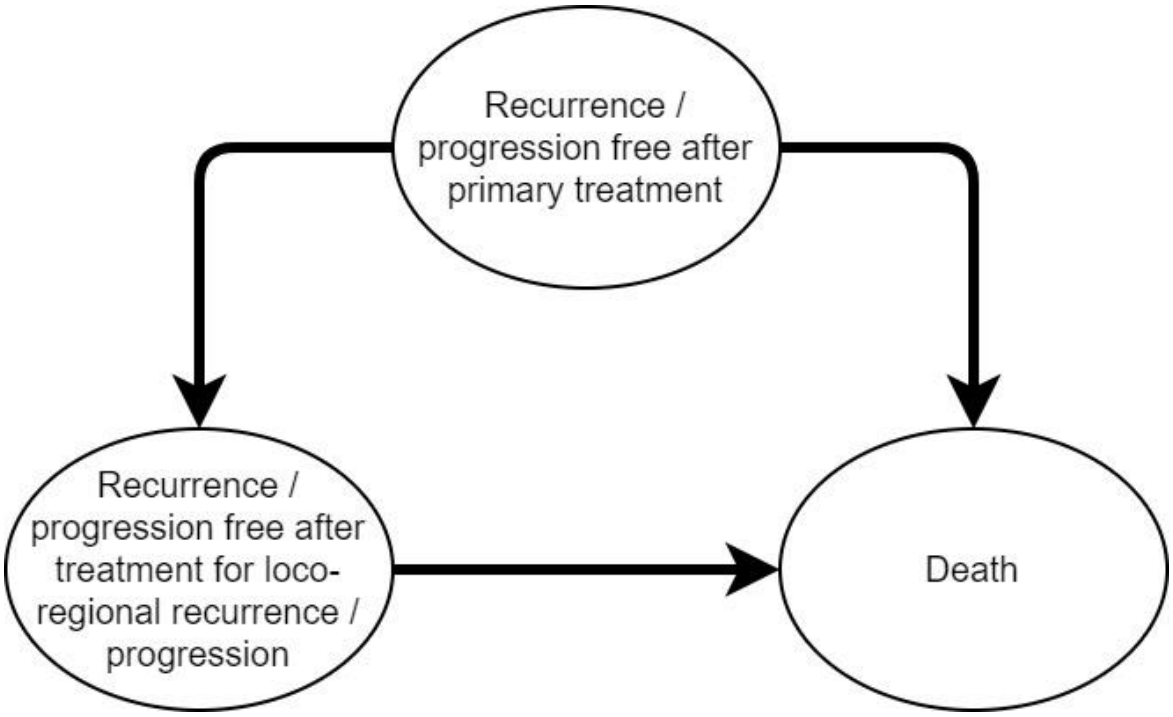

Figure 1 Model Schema

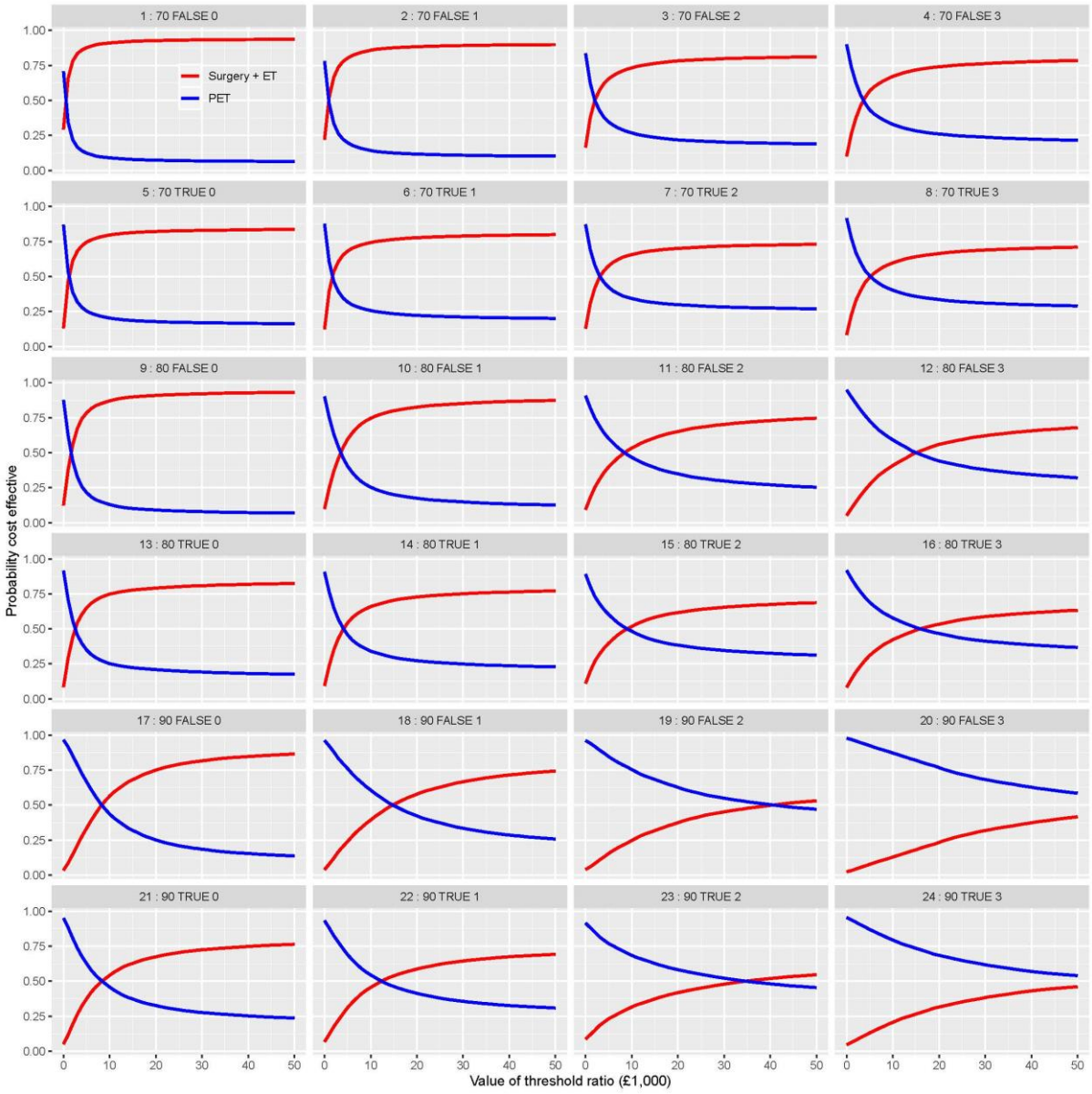

Figure 2 CEAC plots for each subgroup

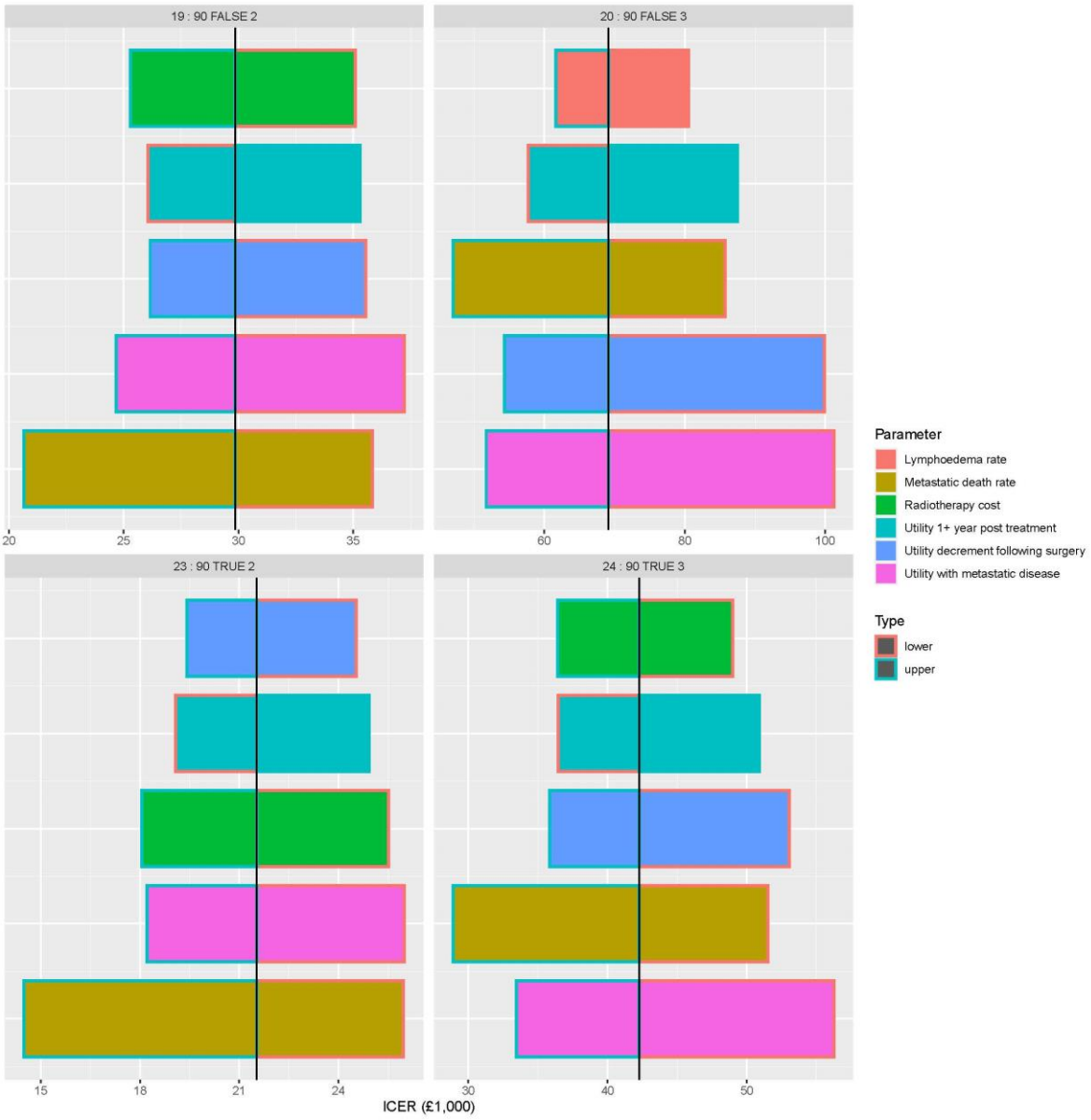

Figure 3 One way sensitivity results for 4 subgroups

Table 1: Model parameter values, standard errors, probability distributions and source

Description	Value	SE	Distribution for PSA	Source
Probability that first event is loco-regional not metastatic	0.232	0.046	Normal	Derived from ATAC trial, Ring 2011(26)

Hazard ratio for relapse / progression or disease control (PET versus surgery)	1.54	0.17	Normal	Morgan 2014(16)
Exponential death rate after distant progression	0.05	0.01	Normal	Chang 2003(23)
Probability of lymphoedema after surgery with SNLB	0.068	0.0136	Beta	Cooper 2011(31)
Probability of lymphoedema after surgery with ALND	0.214	0.0428	Beta	Cooper 2011(31)
Proportion of lymphoedema which is severe (vs mild or moderate)	0.333	0.0666	Normal	Meng 2011(40)
Proportion with osteoporosis age 70-79	0.2	0.04	Beta	Kanis 2007(33)
Proportion with osteoporosis age 80-89	0.4	0.08	Beta	Kanis 2007(33)
Proportion with osteoporosis age 90+	0.670	0.134	Beta	Kanis 2007(33)
Proportion of surgery patients having mastectomy vs BCS age 70-79	0.317	0.012	Beta	Morgan 2020(17)
Proportion of surgery patients having mastectomy vs BCS age 80+	0.513	0.022	Beta	Morgan 2020(17) Horgan 2019(29)
Proportion of patients having SNLB positive	0.030	0.008	Beta	Morgan 2020(17)
Proportion of BCS subsequently having PMRx	0.175	0.035	Beta	Expert opinion
Proportion of patients having BCS & PMRx who then have mastectomy	0.021	0.004	Beta	Morgan 2020(17)
Proportion of patients who get ALND as	0.146	0.008	Beta	Morgan 2020(17)

part of initial surgery				
Proportion of patients having BCS + ALND who have separate PMRx	0.10	0.02	Beta	Expert opinion
Proportion of surgery patients who get radiotherapy (under 90s only)	0.58	0.01	Beta	Morgan 2020(17)
Proportion of patients who get surgery after LRRP (Comorbidity score 0)	0.73	0.146	Beta	Lavelle 2012(35)
proportion of patients who get surgery after LRRP (Comorbidity score 1)	0.66	0.132	Beta	Lavelle 2012(35)
Proportion of patients who get surgery after LRRP (Comorbidity score 2+)	0.49	0.098	Beta	Lavelle 2012(35)
Proportion of PET patients having surgery after LRRP for which it is BCS	0.33	0.066	Beta	Expert opinion
Proportion of ET as aromatase inhibitors (vs Tamoxifen)	0.5	0.1	Beta	Assumed
Probability of chemotherapy related death during 6 month treatment	0.0037	0.00074	Beta	Campbell 2011(30)
Number of radiotherapy fractions	15			Assumed as UK current standard

SE: standard error; PSA probabilistic sensitivity analysis; PET: primary endocrine therapy; SNLB: sentinel lymph node biopsy; ALND: auxiliary lymph node dissection; BCS: breast conserving surgery; PMRx: positive margin re-excision; LRRP: loco-regional recurrence (surgery arm) or progression (PET arm);

Table 2: Resource use parameters

Item	Mean cost £	SE £	Distribution	Source
Fraction of radiotherapy	135	27	Gamma	NHS reference costs 18-19, SC22Z
Overheads for radiotherapy	1049	210	Gamma	Expert advice
Outpatient appointment with clinical oncologist	130	5	Lognormal	NHS reference costs 18-19, WF01A
Mammogram	54	2	Lognormal	NHS reference costs 05-06, inflated to 18-19 using PSSRU
Diagnosis after LRRP	1012	116	Gamma	Hind 2007(34) Tables 23 / 31 inflated to 18-19 using PSSRU
Monthly cost for metastatic disease	494	53	Gamma	Karnon 2007(36) inflated to 18-19 using PSSRU
Monthly costs palliative care (3 months)	1424	192	Gamma	Karnon 2007(36)) inflated to 18-19 using PSSRU
Average monthly ET cost	15	3	Gamma	BNF(32)
Monthly bisphosphanate cost	0.78	0.16	Gamma	BNF(32)
Surgery with ALND for patient with Charlson score 0-1	4340	105	Lognormal	NHS reference costs 18-19, JA38C
Surgery with ALND for patient with Charlson score 2-4	4422	98	Lognormal	NHS reference costs 18-19, JA38B
Surgery with ALND for patient with Charlson score 5+	4827	86	Lognormal	NHS reference costs 18-19, JA38A
Mastectomy with SNLB for patient with Charlson score 0-2	3554	55	Lognormal	NHS reference costs 18-19, JA20F
Mastectomy with SNLB for patient with Charlson score 3-5	3733	61	Lognormal	NHS reference costs 18-19, JA20E
Mastectomy with SNLB for patient with Charlson score 6+	4037	72	Lognormal	NHS reference costs 18-19, JA20D

Breast conservation with SNLB for patient with Charlson score 0-2	2247	40	Lognormal	NHS reference costs 18-19, JA43B
Breast conservation with SNLB for patient with Charlson score 3+	2615	70	Lognormal	NHS reference costs 18-19, JA43A
Positive margin re-excision after BCS	2645	231	Lognormal	NHS reference costs 18-19, JA45Z
Full course of chemotherapy	3786	757	Gamma	OPTIMA prelim report
Average cost of chemotherapy toxicity / adverse events	287	57	Gamma	OPTIMA prelim report + assumptions
Average monthly cost of adverse effect of mild lymphoedema	6.26	0.25	Gamma	Cooper 2011(31) inflated to 18-19 using PSSRU
Average monthly cost of adverse effect of severe lymphoedema	111	4.45	Gamma	Cooper 2011(31) inflated to 18-19 using PSSRU

SE: standard error; NHS: National Health Service, UK; ET: endocrine therapy; SNLB: sentinel lymph node biopsy; ALND: auxiliary lymph node dissection; BCS: breast conserving surgery; PSSRU: Personal Social Services Research Unit inflation indicies

Table 3: Utility parameters

	Mean value	SE	Source
First year disease free after treatment (age 56)	0.744	0.068	Lidgren 2007(37)
Year two onward disease free after treatment (age 58)	0.824	0.018	
After metastatic recurrence (age 56)	0.648	0.064	
Decrement for moving up comorbidity categories	0.070	0.010	Abgorsangaya 2013(39)
Decrement for short term surgical morbidity (3 months)	0.250	0.064	Lovrics 2008(41)
Lifetime decrement for mild-moderate lymphoedema	0.099	0.020	Meng 2011(40)
Lifetime decrement for severe lymphoedema	0.123	0.025	
Decrement during year following chemotherapy	0.043	0.009	Campbell 2011(30)

Table 1. For each patient subgroup, Columns 4-7: Base case incremental cost effectiveness results for Surgery with endocrine therapy versus endocrine therapy only (PET). In every subgroup Surgery is predicted to deliver increased QALYs compared to PET. However, the increase becomes more marginal with increasing age and increasing comorbidity score. There is a corresponding increase in the incremental costs. Columns 8-9: PSA results showing the probability that surgery is cost effective relative to PET at a £20,000 willingness-to-pay threshold.

	Patient subgroup			Deterministic results				PSA results
Sub-group No.	Age	Nodal status	Co-morbidity score	Cost incremental (discounted)	Life years incremental	QALYs incremental (discounted)	ICER Surgery versus PET Discounted (£/QALY)	Probability CE at £20k (%)
1	70	FALSE	0	-88	3.92	1.6322	Surgery dominates	93
2			1	430	3.41	1.3105	328	88
3			2	1012	2.88	0.9998	1,013	78
4			3	1964	2.09	0.7728	2,542	74
5		TRUE	0	1060	3.52	1.5107	702	82
6			1	1336	3.18	1.2608	1,059	78
7			2	1802	2.64	0.9488	1,899	70
8			3	2533	1.95	0.7514	3,371	67
9	80	FALSE	0	935	2.54	1.0489	892	91
10			1	1657	1.68	0.6831	2,426	83
11			2	2330	1.05	0.4030	5,782	66
12			3	3142	0.65	0.2628	11,955	57
13		TRUE	0	1696	2.31	0.9820	1,727	79

14			1	2066	1.66	0.6952	2,971	73
15			2	2527	1.08	0.4328	5,838	62
16			3	3156	0.71	0.3028	10,424	54
17	90	FALSE	0	2570	0.83	0.3862	6,655	76
18			1	3009	0.56	0.2444	12,311	60
19			2	3555	0.33	0.1191	29,852	40
20			3	4199	0.2	0.0607	69,124	27
21		TRUE	0	2703	0.87	0.4205	6,429	68
22			1	2940	0.63	0.2891	10,167	60
23			2	3367	0.4	0.1563	21,533	44
24			3	3933	0.25	0.0931	42,268	34