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Supplementary Material

1. Baseline hazard of recurrence (patients with surgery)

The hazard of recurrence for surgery patients was derived from the ATAC trial. Ideally, this would be based on individual patient data (IPD) but as this was not available the method of Guyot *et al* [ref] was used to reconstruct the IPD from published Kaplain Meyer (KM) estimates.

Ring et al [ref], Figure 1A displays the Kaplan-Meier estimate of the time to recurrence for women in the ATAC trial stratified by age at diagnosis (<60, 60-70, 70-75, >75), pooled over both treatment arms. The Guyot algorithm was used to extract an estimate of the underlying IPD. Numbers at risk were not reported in the original manuscript but were provided at biannual intervals by the study authors (I Sestak, personal communication 2011. Data provided as academic in confidence). The recreated Kaplan-Meier estimates for time-to-recurrence for the age groups 70-74 and 75+ are shown in Figure S1. It can be seen that risk of recurrence in the first two years after randomisation was almost identical for women aged 70-74 and women aged 75 and over. However, from this time the survival curves diverge, with older women experiencing a higher rate of recurrence. At 10 years post-treatment the absolute difference in the incidence of recurrence was approximately 8%.

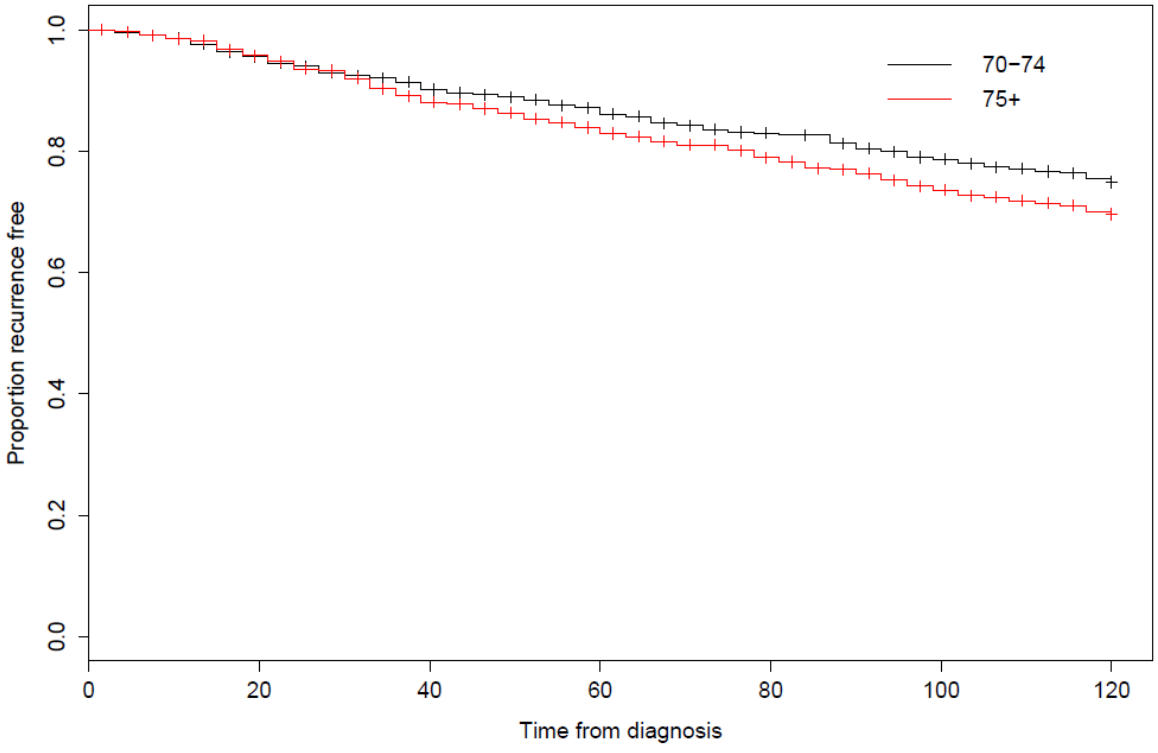

Figure S1 Kaplan-Meier curves for time to recurrence for patients aged 70-74 and 75+, based on extracted IPD from Ring et al [ref].

An estimate of the hazard function for recurrence for patients aged 75 and over is shown in Figure S2. The dashed line shows the hazard estimated using a piecewise exponential distribution over 12 month intervals, with a smoothed estimate superimposed. It can be seen from the plot that hazard increased from time of diagnosis for a period of about 24-36 months, from which time it was

approximately constant for the remainder of the observation period of 120 months. It was therefore decided to model the baseline hazard separately for the period immediately after treatment and for later times using a piecewise model. To estimate the hazard function at the population level, a parametric curve was fit to the extracted IPD. Separate functions were specified for the first two years and subsequent years. Parametric distributions were fit to these two time periods using maximum likelihood.

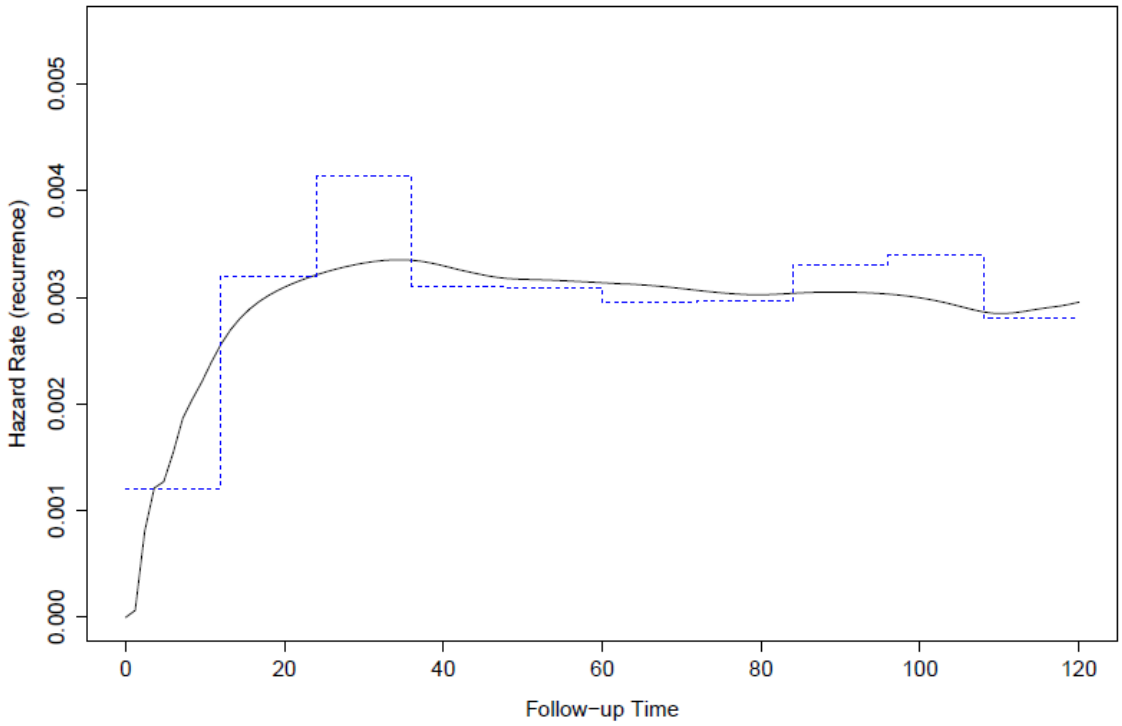

Figure S2 Estimate of the hazard of recurrence for patients aged 75+ treated with surgery and adjuvant endocrine therapy,, based on extracted IPD from Ring et al [ref].

In the first 24 months post-diagnosis, the hazard rate appears to be monotonic increasing (Figure S2). Weibull, log-logistic and log-normal distributions were fit to the data for the initial 24 month period along with the exponential distribution. The Weibull, log-normal and log-logistic distributions result in almost identical survival curves and all fit the observed data closely. The exponential model slightly under-estimates the Kaplan-Meier estimator for part of the 24 months period, however this discrepancy is never greater than 0.6%. .Although the Weibull would normally be the most suitable choice, the exponential distribution was chosen for two reason: Firstly, the difference in absolute probability of recurrence by any time point in this period between the two distributions was small, and there was no difference by t = 24. As a result it was thought unlikely that using a more flexible model over this time period would impact substantially on cost-effectiveness results. Secondly, using a piecewise exponential model significantly simplified the derivation of subgroup specific survival distributions as, conditional on covariates, estimates of hazard rates in each time period are asymptotically independent. The estimated scale parameters was 461 which corresponds to a hazard rate of 0.0022.After two years from randomisation, the hazard of recurrence appeared to be approximately constant, suggesting the exponential distribution as an appropriate choice of parametric model. Under this model, the scale parameter was estimated to be 323 which corresponds to a hazard rate over this period of 0.0031.

Separate KM curves stratified by age and lymph node status and based on the ATAC data were not available. Therefore a calibration approach using a Metropolis Hastings algorithm was used to make

adjustment for these patient characteristics. The data reported by Ring et al suggested that for the first two years after surgery the hazard of recurrence was independent of age. As a result it was assumed that for the first two years of the model, the hazard of recurrence was dependent on nodal status alone, whilst for subsequent years, on both age at diagnosis and nodal status. Assuming that for each subgroup the hazard of recurrence is constant for the first two years and for subsequent years, this leads to the following formulation of the log-hazard of recurrence,

$$\log\big(h(t;\theta,\boldsymbol{x_i})\big) = \begin{cases} \alpha_1 + \beta_1 x_1 & t < 24 \\ \alpha_2 + \beta_2 x_1 + \gamma_2 x_2 & t \geq 24 \end{cases}$$

where t is time in months from randomisation, $\boldsymbol{x_i}$ is the vector of patient level covariates ($x_1 = 0$: nodal negative, $x_1 = 1$: nodal positive; $x_2 = 0$: age group 75-79, …, $x_2 = 3$: age group 90+), and $\theta = (\alpha_1, \alpha_2, \beta_1, \beta_2, \gamma_2)$ is the vector of model parameters. Full details of the parameter estimation procedure are available on request. The identified parameters are:

$$\alpha_1 = -6.561,\ \beta_1 = 0.847$$

$$\text{covariance: } \begin{matrix} 0.00692 & \\ -0.00284 & 0.00692 \end{matrix}$$

$$\alpha_2 = -6.269,\ \beta_2 = 0.850,\ \gamma_2 = 0.205$$

$$\text{covariance: } \begin{matrix} 0.00545 & & \\ -0.00333 & 0.00584 & \\ -0.00585 & 0.00018 & 0.0124 \end{matrix}$$

Convergence was only achieved when estimating the parameters for the two time periods separately. The drawback of this is that the full covariance between all five parameters is unspecified. The resulting survival curves are shown in Figure S3.

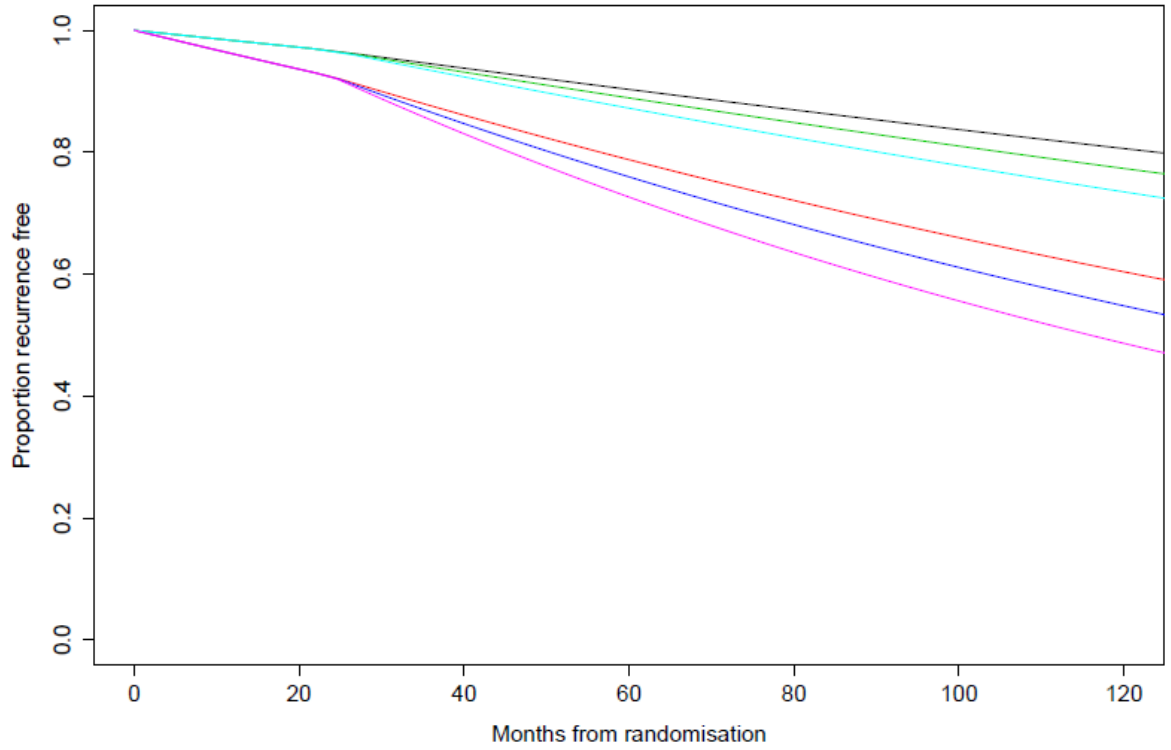

Figure S3 Expected time to recurrence curves derived for node negative and node positive disease (high group and low group respectively) further sub-grouped by increasing age (high to low in each group).

2. Costs and disutility associated with breast cancer mortality

It was assumed in the model that breast cancer mortality (BCM) occurs if and only if a patient spends time with metastatic disease (Mets). The associated costs and disutility are incorporated as one off adjustments at the time of BCM.

BCM for someone with Mets was assumed to occur according to an exponential distribution with constant rate 0.05 per month [chang et al]. This equates to a mean survival with Mets of 20 months. The costs of BCM was therefore calculated as:

$$\text{Cost}_{\text{BCM}} = \text{Cost}_{\text{Diagnosis}} + (20-3)\text{Cost}_{\text{Living with Mets}} + 3\text{Cost}_{\text{Terminal phase}}$$

With the latter two costs being derived from [Karnon].

The one-off utility decrement applied at the time of BCM was calculated as:

$$\delta U_{\text{BCM}} = 20(U_S^{age} - U_M^{age})$$

Where U_S^{age}, and U_M^{age} are respectively the age adjusted utility values for a patient during second and subsequent years after treatment and the age adjusted utility for a patient with metastatic disease as derived in [Lidgren].

3. Partitioned survival model algorithm

Given a chosen set of patient characteristics (i.e. Age from {70,80,90}, Charlson score from {0,1,2,3+}, Nodal status from {-,+}) and for both treatment arms:

1. Load the corresponding hazards for BCM and OCM calculating using the prognostic model [validation paper].
2. Derive hazard of recurrence (surgery arm) / progression (PET arm). Though the natural history is different in the arms the hazard is assumed identical.
3. Sum the three hazards above to calculate the total hazard of no-longer being recurrence / progression free and convert to a survivor function (PFS) in the usual way.
4. Similarly, sum the two hazards from (1) to derive an all-cause mortality (ACM) survivor function.
5. Subtract the survivor function in (3) from that in (4) to calculate the proportion of patients alive and with progressive / recurrent disease.
6. Divide the recurrence hazard in (2) by that in (3) to get the instantaneous probabilities that a new event is a recurrence / progression as opposed to a death.
7. Divide the BCM hazard in (1) by the ACM hazard in (4) to get the instantaneous probabilities that any death is BCM.
8. The above allow the calculation at each time point of:
    a. New BCM deaths
    b. New OCM deaths
    c. New progression / recurrence events
9. Multiply elementwise PFS by schedule of primary treatment / follow up costs
10. Multiply the average cost of treatment for new progression / recurrence by the number of such new events at each time.
11. Multiply elementwise the proportion with recurrent / progression from (5) by the schedule of average secondary follow up costs.
12. Multiply new BCM deaths by the total average cost of metastatic disease and BCM.
13. Add together the results of (9)-(12) to get the total costs for each month modelled.
14. Sum the amounts in (13) without and with discounting to get the total costs.
15. Multiply elementwise PFS by age-adjusted utility schedule (also adjusted, as appropriate, for short-term surgery decrement and comorbidity and lymphoedema decrements)
16. Multiply elementwise the proportion with recurrent / progression from (5) by the similarly appropriate utility schedule.
17. Multiply new BCM deaths by the assumed on-off utility decrement (representing the total decrement over the average length the terminal metastatic phase.
18. Sum the monthly utilities / decrements calculated in (15)-(17) to get the total utility gained in each month.
19. Convert the utilities to QALYs and sum without and with discounting to get total QALYs.
20. Perform incremental analysis in the usual way.

4. Further results

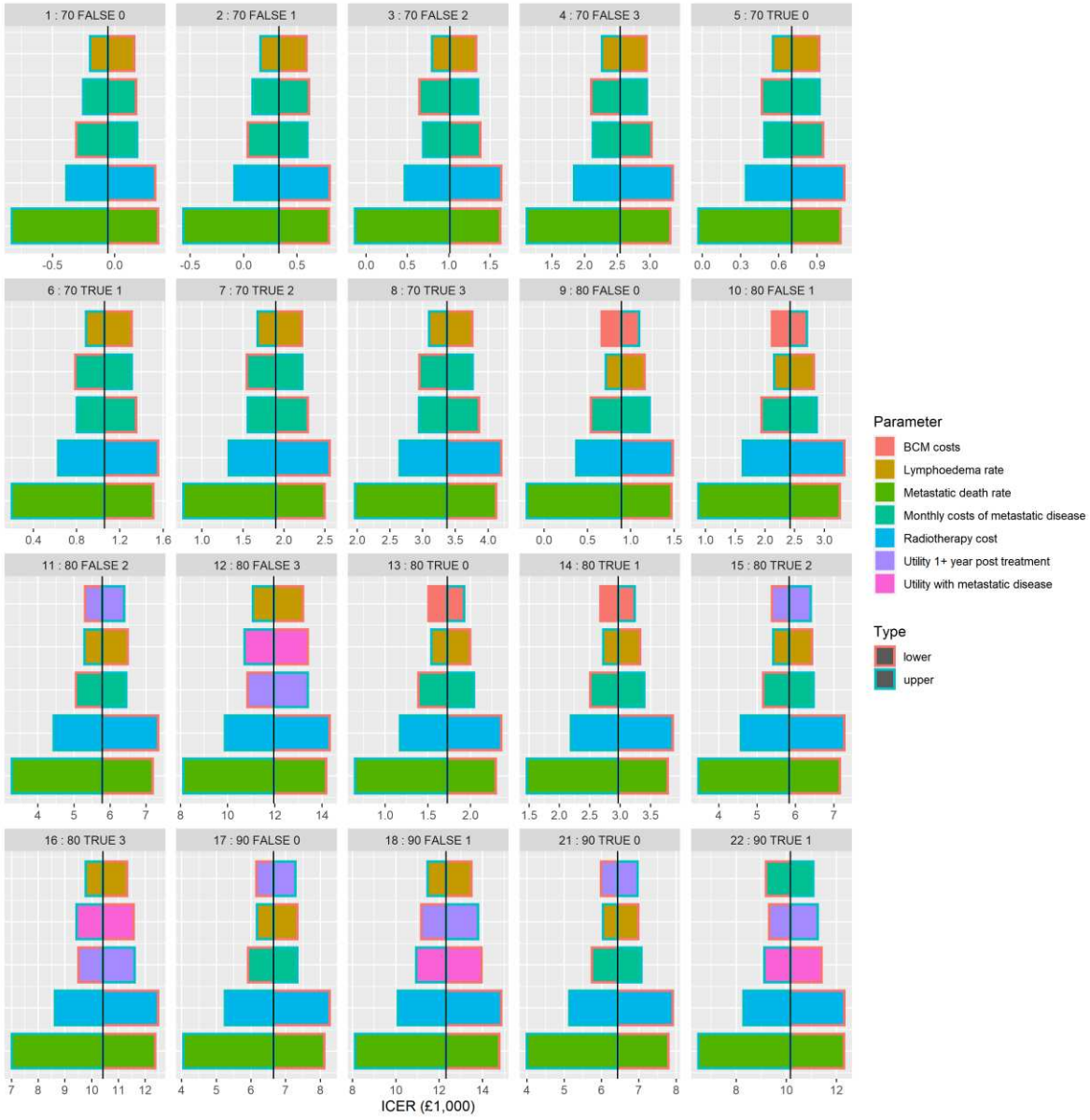

Figure 4 One way sensitivity results for the subgroups where the deterministic incremental QALYs was greater than 0.2. These were also the subgroups where Surgery was cost-effective at the £20,000 threshold according to the deterministic analysis. The plots show that the largest uncertainty for each subgroup is associated with the monthly death rate for patients who have metastatic cancer. Nevertheless, for these subgroups the cost-effectiveness decision at the £20,000 threshold isn't altered by the variations made to this parameter.

Table S1 Partitioned survival model: Comparison of base case incremental analysis to mean PSA incremental analysis.

				Deterministic analysis			Mean PSA analysis		
Sub-group No.	Age	Nodal status	Co-morbidity score	Cost incremental (discounted)	QALYs incremental (discounted)	ICER Surgery versus PET Discounted (£/QALY)	Cost incremental (discounted)	QALYs incremental (discounted)	ICER Surgery versus PET Discounted (£/QALY)
1	70	FALSE	0	-88	1.6322	Surgery dominates	31	1.655	19
2			1	430	1.3105	328	477	1.41	338
3			2	1012	0.9998	1,013	1247	0.997	1,251
4			3	1964	0.7728	2,542	2082	0.795	2,619
5		TRUE	0	1060	1.5107	702	1322	1.454	909
6			1	1336	1.2608	1,059	1639	1.238	1,324
7			2	1802	0.9488	1,899	2229	0.865	2,576
8			3	2533	0.7514	3,371	2956	0.67	4,413
9	80	FALSE	0	935	1.0489	892	940	1.072	877
10			1	1657	0.6831	2,426	1560	0.743	2,099
11			2	2330	0.4030	5,782	2262	0.442	5,123
12			3	3142	0.2628	11,955	3050	0.296	10,294
13		TRUE	0	1696	0.9820	1,727	1873	0.938	1,998
14			1	2066	0.6952	2,971	2269	0.675	3,361
15			2	2527	0.4328	5,838	2775	0.414	6,699
16			3	3156	0.3028	10,424	3390	0.287	11,821
17	90	FALSE	0	2570	0.3862	6,655	2434	0.421	5,783
18			1	3009	0.2444	12,311	2781	0.286	9,731
19			2	3555	0.1191	29,852	3343	0.147	22,810
20			3	4199	0.0607	69,124	3971	0.083	47,977
21		TRUE	0	2703	0.4205	6,429	2761	0.421	6,563
22			1	2940	0.2891	10,167	2948	0.301	9,791
23			2	3367	0.1563	21,533	3451	0.156	22,144
24			3	3933	0.0931	42,268	4080	0.086	47,248

Table S2 For each subgroup, are shown 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. The numbers stated are per 1,000 patients as predicted by the partitioned survival model.

			PET						Surgery					
Age	**Como score**	**Nodal status**	**Local progression by Yr2**	**Local progression by Yr5**	**BCM by Yr2**	**BCM by Yr5**	**OCM by Yr2**	**OCM by Yr5**	**Local recurrence by Yr2**	**Local recurrence by Yr5**	**BCM by Yr2**	**BCM by Yr5**	**OCM by Yr2**	**OCM by Yr5**
70	0	0	12	28	43	161	20	66	8	20	11	44	20	71
70	0	1	27	62	79	248	19	62	18	44	33	109	20	68
70	1	0	12	27	60	182	30	98	8	19	16	50	31	106
70	1	1	26	59	110	279	29	91	18	42	46	124	30	101
70	2	0	12	27	58	187	46	147	8	19	15	52	47	160
70	2	1	26	57	106	285	45	136	18	41	44	128	46	152
70	3	0	11	25	62	196	70	216	8	18	16	55	72	235
70	3	1	26	55	114	299	68	198	17	39	48	135	70	223
80	0	0	11	33	63	203	58	181	8	24	16	56	59	198
80	0	1	26	70	115	308	56	167	17	52	48	139	58	188
80	1	0	11	31	87	222	87	257	7	22	23	63	90	287
80	1	1	25	63	157	336	83	231	17	48	67	154	88	269
80	2	0	11	28	83	215	132	364	7	20	22	61	136	406
80	2	1	25	59	150	326	126	328	17	44	64	150	133	381
80	3	0	11	25	86	208	196	491	7	18	23	59	202	550
80	3	1	24	52	156	318	187	441	16	39	66	147	198	514
90	0	0	11	34	88	223	164	430	7	25	23	64	170	483
90	0	1	24	69	159	338	157	384	16	53	68	157	166	450
90	1	0	10	28	118	230	236	547	7	21	32	66	249	630
90	1	1	22	55	210	350	221	478	15	44	92	165	240	577
90	2	0	10	22	107	196	342	685	6	17	29	56	358	777
90	2	1	21	45	192	305	321	604	15	35	83	143	346	718
90	3	0	9	17	103	164	472	791	6	12	28	47	496	888
90	3	1	19	34	185	263	443	704	13	26	81	122	478	824

Table S3 For each subgroup is shown the breakdown of costs in each treatment arm. Costs are in GBP £. Surgery and Progression free follow up are average cost per patient. Post-progression treatment (PET) and post-recurrence treatment (Surgery) are cost per patient experiencing progression / recurrence. Metastatic disease and palliative treatment is per breast cancer mortality. Surgery costs decreases with age due to the reduced proportion received BCS in contrast to Mastectomy. Other costs reduce with age due to reduced survival.

			PET			Surgery			
Age	**Nodal status**	**Como score**	**Progression-free follow up**	**Post-progression treatment**	**Metastatic disease and palliative treatment**	**Surgery**	**Progression-free follow up**	**Post-progression treatment**	**Metastatic disease and palliative treatment**
70	FALSE	0	5972	5617	13687	5659	8582	6457	13687
		1	5583	5593	13687	5659	8489	6368	13687
		2	4728	5144	13687	5673	8363	5982	13687
		3	3868	4796	13687	5937	8452	5522	13687
	TRUE	0	4871	5461	13687	5659	8391	6282	13687
		1	4543	5449	13687	5659	8298	6214	13687
		2	3880	4947	13687	5673	8190	5757	13687
		3	3221	4615	13687	5937	8299	5306	13687
80	FALSE	0	4101	5033	13687	5251	7840	5820	13687
		1	3384	4685	13687	5251	7651	5304	13687
		2	2696	3989	13687	5265	7465	4463	13687
		3	2127	3767	13687	5497	7473	4103	13687
	TRUE	0	3330	4886	13687	5251	7665	5644	13687
		1	2776	4570	13687	5251	7487	5180	13687
		2	2276	3883	13687	5265	7330	4354	13687
		3	1835	3691	13687	5497	7361	4034	13687
90	FALSE	0	2325	4220	13687	5251	7330	4685	13687
		1	1802	3864	13687	5251	7087	4242	13687
		2	1416	3270	13687	5265	6852	3552	13687
		3	1083	3225	13687	5497	6828	3451	13687
	TRUE	0	1963	4153	13687	5251	7198	4622	13687
		1	1527	3816	13687	5251	6963	4202	13687
		2	1238	3227	13687	5265	6762	3519	13687
		3	966	3194	13687	5497	6765	3428	13687

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