Modelling the cost-effectiveness of alternative upper age limits for breast cancer screening in England and Wales

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Appendix 1

Here, we briefly summarise the main natural history model structure, evidence used and calibration method. Full details are available in the full report available through the Web (http://www.sheffield.ac.uk/polopoly_fs/1.395824!/file/RachidRafia.pdf).

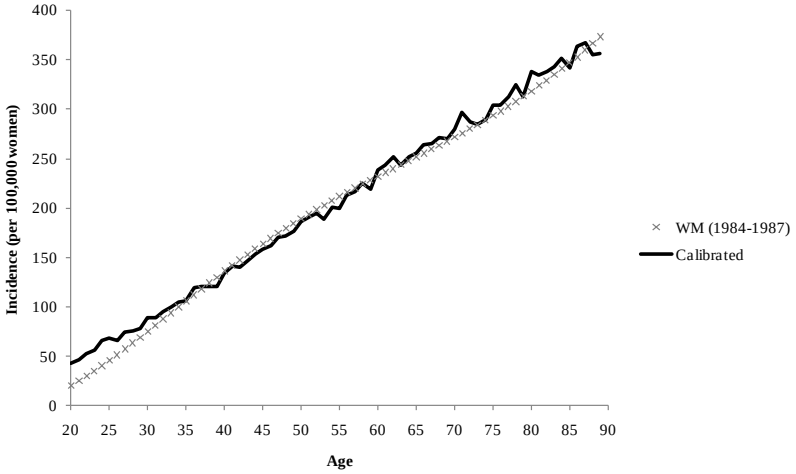
The natural history of breast cancer is progressive. Patients who eventually develop cancer enter a preclinical state in which the disease has no symptoms but can be diagnosed through screening, after which the disease presents naturally. The disease progression model includes no disease alongside five main breast cancer health states – carcinoma in situ, local, regional (1-3 nodes involved), regional (4+ nodes), and distal disease.

We represented the disease progression of breast cancer in a mathematical form and we used published and unpublished data to inform the model structure and input parameters. However, whilst data were available for some of the input parameters, some model parameters are not directly measurable, such as the time to the preclinical state.

A calibration approach was therefore employed to estimate unobservable parameters, using an iterative process. This involved imputing initial values for the unknown parameters and simulating results given these values. Predictions are then compared with the actual data available. The values for the unknown parameters are then adjusted iteratively (using the maximum likelihood method) until the simulated results match closely to the observed data sets. The model of fit was assessed comparing the proportions of cases falling into different categories matching the target data (e.g. predicted v actual proportions of local, regional and distant metastasis at presentation) and the statistical likelihood (calculated using a multinomial model).
The model was fitted to the following observed data; prognostic profile (tumour size, grade, ER, nodal status and number of positive nodes) at diagnosis in women aged over 70 from the West Midlands Cancer Intelligence Unit (n=6,859)[1] and the Eastern Cancer Registry Information Centre (n=3,757)[2], age-related breast cancer incidence in the West Midlands between 1988 to 1994[3] (before the implementation of screening), and routine data from the NHSBSP on screening tumour size at detection in women aged over 60 years (as data were limited in women aged over 70 years) [4].

Overall, a reasonably good fit to the observed data was obtained for the values used for the unknown parameters resulting from the calibration of the model. As shown in Figure 1, the predicted age specific breast cancer incidence closely matched the incidence data observed in the West Midlands.

Figure 1: Calibrated incidence versus Observed incidence before screening



Similarly, a reasonably good fit was observed for the screening data[4] overall (Figure 2 – 4).

Figure 2: Calibrated tumour size at detection vs observed distribution from the NHSBSP (2006) in women aged 60-64 years old (previous attenders)

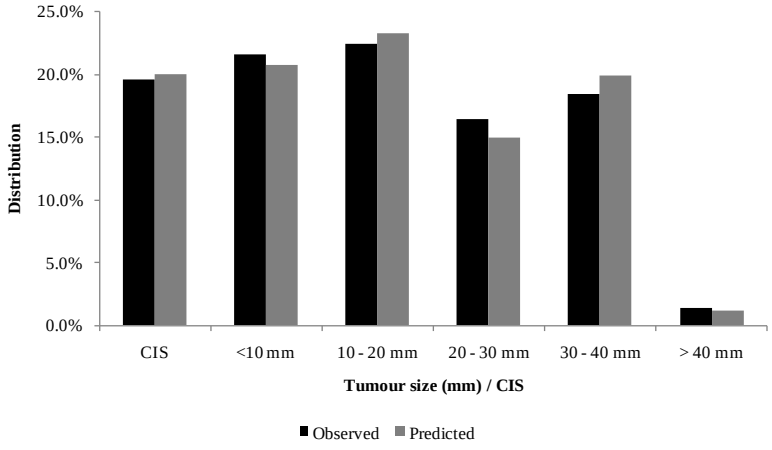


Figure 3: Calibrated tumour size at detection vs observed distribution from the NHSBSP (2006) in women aged 65-69 years old (previous attenders)

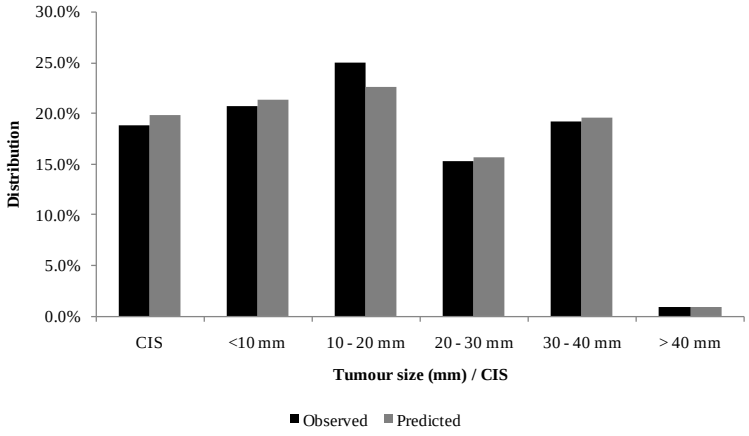
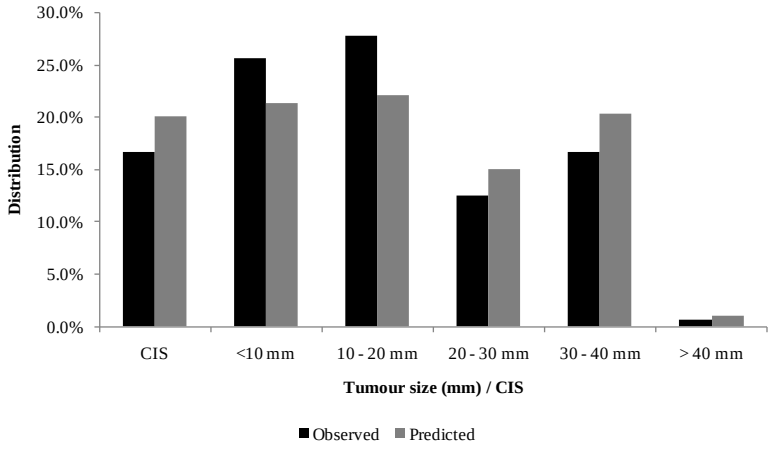


Figure 4: Calibrated tumour size at detection vs observed distribution from the NHS BSP (2006) in women aged 70 years old (previous attenders)



Finally, the model was also calibrated against natural history data from the West Midlands and East Anglia for older women presenting due to clinical symptoms of breast cancer. The fit was found to be reasonably good when comparing the proportion of elderly women by grade, nodal status, ER status and tumour size (Figure 5 – 7).

Figure 5: Calibrated distribution of patient by grade, nodes and ER in symptomatic women vs observed distribution from the WMCIU in women aged 70+

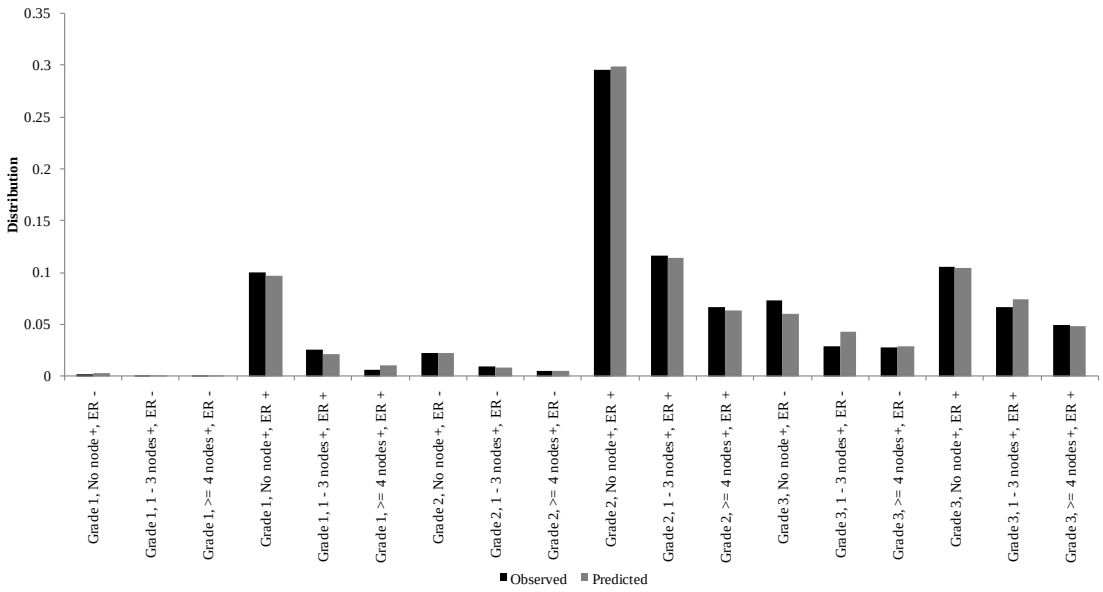


Figure 6: Calibrated tumour size distribution among women presenting symptomatically vs observed distribution from the WMCIU in women aged 70+

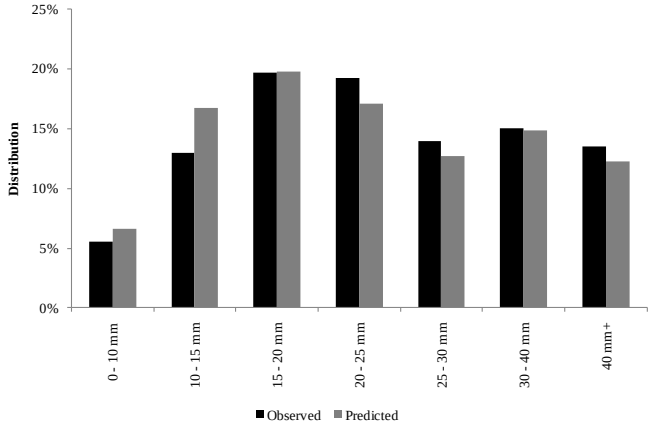
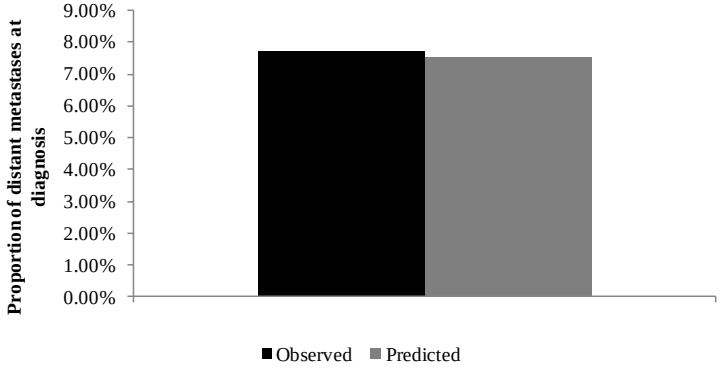


Figure 7: Calibrated proportion of patients presenting from distant metastasis vs observed proportion from the ECRIC in women aged 70+



Appendix 2

a) Survival in women diagnosed with invasive cancer

A parametric survival regression model was constructed among women diagnosed with invasive breast cancer but no metastasis. Included covariates were pre-specified and consisted of prognostic profiles that were believed to affect treatment choice and therefore survival in older women. This was governed by the fact that there is a direct relationship between prognostic profile and treatment and treatment and survival.

The estimated survival model uses ages (in months), tumour size (in mm), number of positive nodes (0, 1-3, 4+) and ER status as covariates. We also included the interaction between age at diagnosis and tumour size to account for the fact that tumour size is greater as the age at diagnosis increased. We did not include grade as a covariate for two reasons; first, our model did not include the direct shift in grade associated to screening; and finally there is a relationship between tumour size, nodal status and grade.

The model was constructed among 3,057 women. The coefficients for age, tumour size and nodal involvement were negative. This indicates that women would have a worse survival as the age or the tumour size or the nodal involvement increase. The coefficient for ER status was however positive, indicating that women with ER^{+ve} tumours had a better survival compared to women with ER^{-ve} tumours.

A Log-Logistic parametric survival model was fitted to the data for the central case. This was selected as this was shown to fit best the data using the AIC and BIC criteria calculated in Stata and behaviour of the plotted curve to KM data.

Equation 1: Log Logistic regression model to predict the age at death among women diagnosed with invasive cancers but no metastasis

No. of subjects =	3057	Number of obs. =	3057
No. of failures =	775		
Time at risk =	142389	LR chi2(6) =	440.74
Log likelihood =	-2132.1589	Prob > chi2 =	0.0000

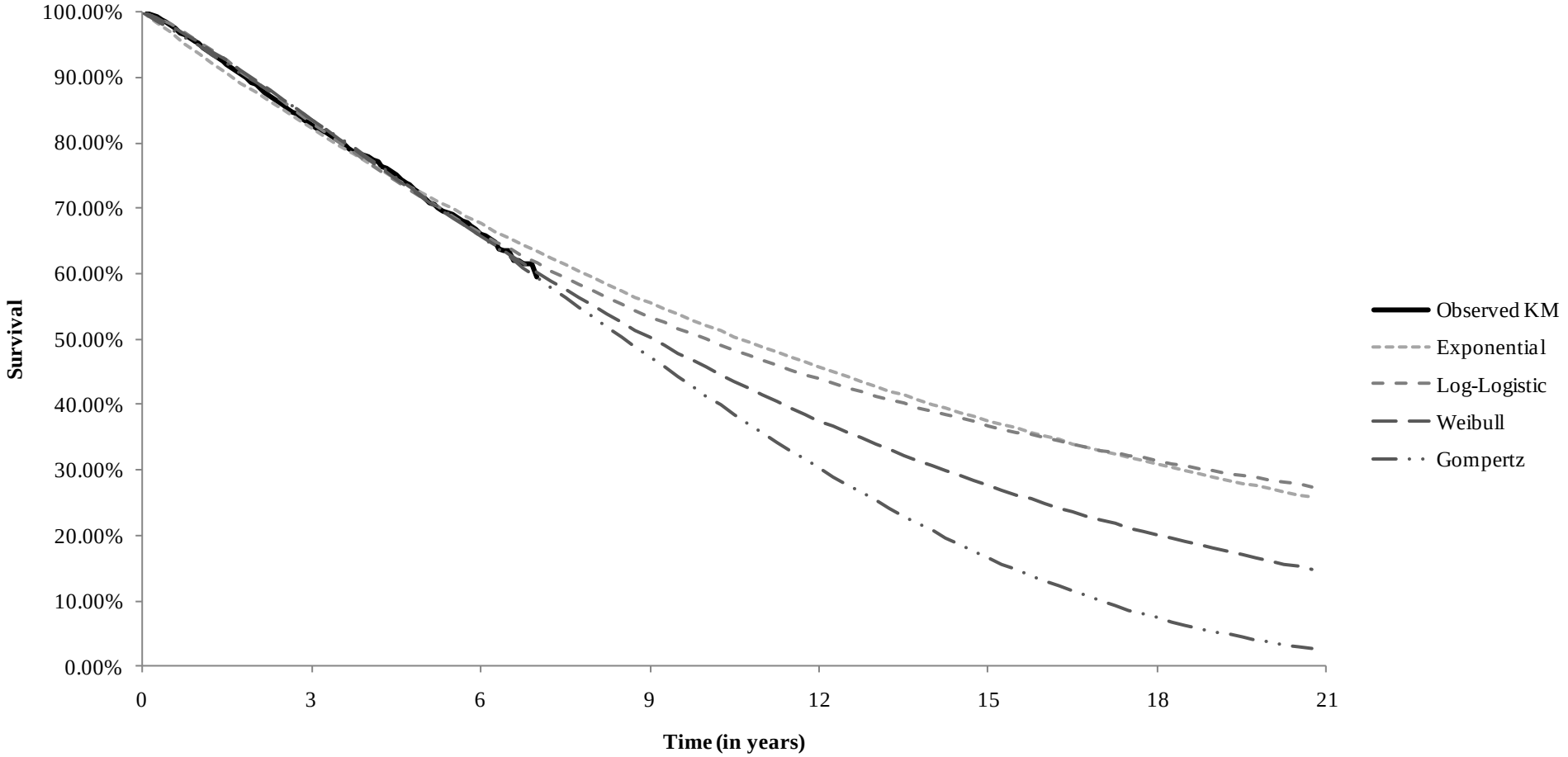
_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ageatdiagn~s	-.0056413	.0009211	-6.12	0.000	-.0074467	-.0038359
invsize	-.0308522	.0248117	-1.24	0.214	-.0794823	.0177779
agesize	.0000193	.0000263	0.73	0.464	-.0000323	.0000708
_Inodes_2	-.2889889	.0717084	-4.03	0.000	-.4295347	-.1484431
_Inodes_3	-.9108843	.0786228	-11.59	0.000	-1.064982	-.7567866
ER	.5415645	.0708132	7.65	0.000	.4027732	.6803558
_cons	10.09477	.8689685	11.62	0.000	8.391622	11.79792
/ln_gam	-.3962368	.0315016	-12.58	0.000	-.4579789	-.3344947
gamma	.6728474	.0211958			.6325608	.7156996

Table 1: AIC and BIC (invasive cancer) by distribution type

	AIC	BIC
Exp	4,345.51	4,387.68
Weib	4,284.06	4,332.26
Gomp	4,301.68	4,349.88
Log-Log	4,280.32	4,328.52

The observed KM was plotted to the predicted survival time using different parametric distributions in Figure 8 (before adjustment for covariates).

Figure 8: Plot of observed and predicted all cause survival in women with breast cancer diagnosed with invasive cancer (n = 3,057)



b) Survival in women diagnosed with distant metastasis

We also constructed a survival regression model to estimate the age at death among women diagnosed with distant metastasis. The statistical model included only age as a covariate and was constructed based on a small sample size of 21 women. The small sample size is likely to bias results. However, the median survival for these patients was found close to the survival expected for this group of women; i.e. 30 months (95% CI: 9 – 45).

Equation 2: Exponential regression model to predict the age at death among women diagnosed with distant metastasis

No. of subjects =	21	Number of obs =	21
No. of failures =	16		
Time at risk =	599	LR chi2(1) =	0.93
Log likelihood =	-30.128859	Prob > chi2 =	0.3345

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ageatdiagn~s	.0044218	.0045493	0.97	0.331	-.0044947	.0133383
_cons	-7.866117	4.402877	-1.79	0.074	-16.4956	.7633635

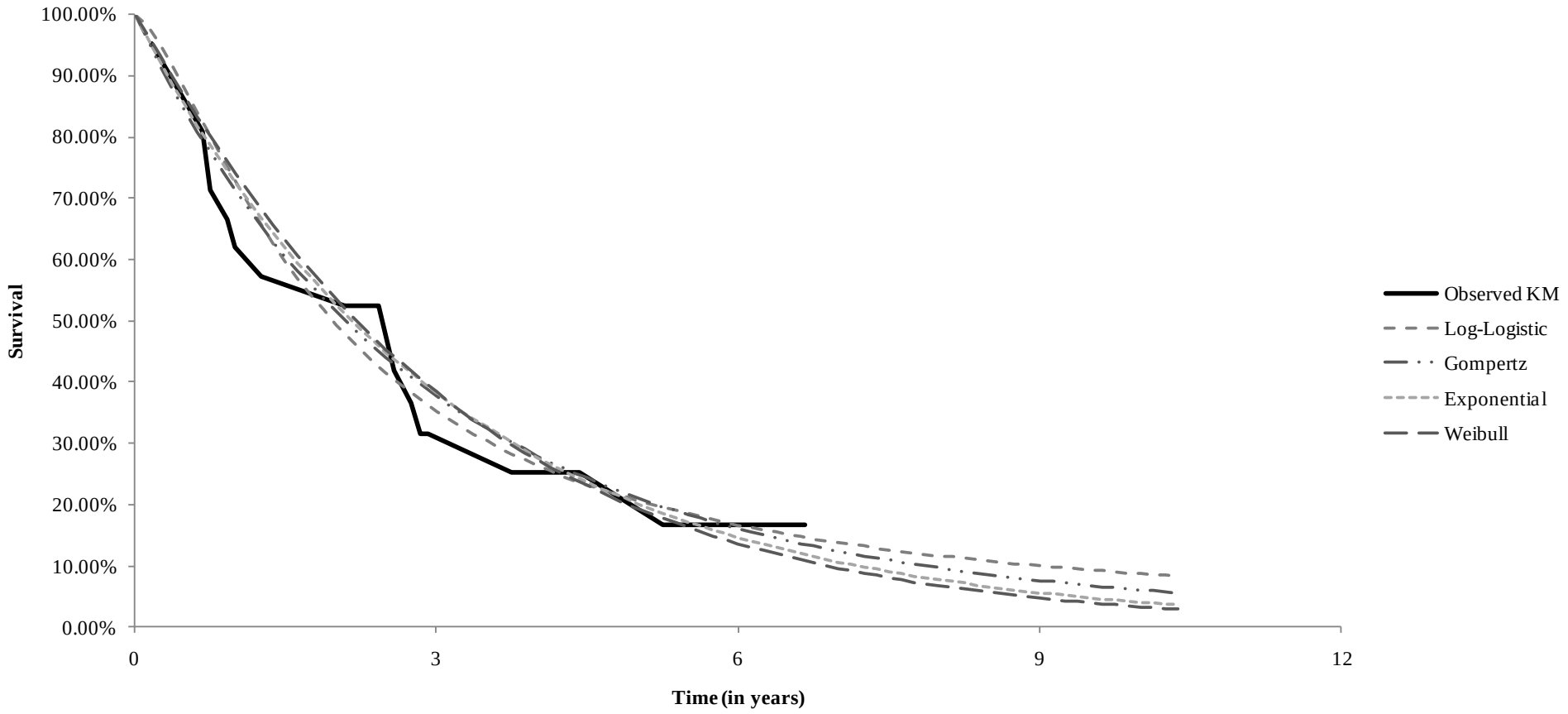
The coefficient for age was negative indicating that survival was expected to decrease as age increased. Using the AIC and BIC (Table), an exponential distribution was fitted to the survival in women diagnosed with disease metastasis for the central case. Other distributions were also tested in sensitivity analysis.

Table 2: AIC and BIC (metastasis) by distribution type

	AIC	BIC
Exp	64.26	66.35
Weib	66.16	69.29
Gomp	66.23	69.36
Log-Log	65.90	69.04

The observed KM was plotted to the predicted survival time using different parametric distributions in Figure 9 (before adjustment for covariates).

Figure 9: Plot of observed and predicted all cause survival in women with breast cancer diagnosed with distant metastasis (n = 21)



Appendix 3

In the model, for the basecase, due to random variability within the simulation runs, some women can be sampled as dying earlier from breast cancer in the screening arm compared with the non extended screening arm, especially if the time between screen-detection and the age at which the cancer would present symptomatically is long enough.

This may be clinically plausible as for some women, early diagnosis may be harmful. Up to date, there is no strong evidence of this effect; however, a conservative approach was used in our model basecase, and we assumed that this was plausible i.e. that screening can lead to earlier detection, but can also lead to earlier death for some women.

Two alternative scenarios are presented relaxing this assumption:

- *Scenario 1:* screening leads to earlier detection but cannot lead to premature death at the individual level. Women are assumed to die at the same time as if not detected through screening. The survival is applied from the age at screen detection using the prognostic profile at diagnosis. If the sampled age at death due to breast cancer assuming screening (ex 89) is lower than the sampled age at death for the "same" woman in the absence of screening (ex 92), the woman is assumed to die at the same age she would have died in the absence of screening (here 92 years old).
- *Scenario 2:* screening leads to earlier detection but necessarily translates into a survival benefit. In this scenario, the survival in case of screen-detection is applied from the age at which the women would present due to clinical symptoms using the prognostic profile from the point at screen detection. Therefore, as screening leads to earlier detection, screening would ultimately lead to an improvement in the prognostic profile and therefore improved survival compared to the absence of screening.

Appendix 4

Logistic regression models were constructed to calculate the likelihood of resource used from the ECRIC dataset adjusted for a set of covariates (tumour size, grade, ER status, nodal involvment, age, distant metastasis). Given the impossibility to have direct access to the data, covariates were pre-specified and validated by clinical opinion. The estimated models allowed calculation of the probability of resource use for each woman. A random number was then generated and the women were assumed to be treated if the probability was greater than the generated random number.

- *Probability of surgery*

We constructed a statistical model to predict the probability of receiving surgery post-diagnosis in elderly women only. The model uses age (in years), tumour size (in mm) and the presence of distant metastasis as the main determinants (Equation 3). The coefficient for age, tumour size and presence of distant metastasis was negative. This indicated that the probability of surgery decreases as the patient's age or tumour size increase or in the presence of distant metastasis.

Equation 3: logistic regression model to predict the likelihood of surgery

Logistic regression	Number of obs =	2621
	LR chi2(3) =	561.99
	Prob > chi2 =	0.0000
Log likelihood = -1050.8181	Pseudo R2 =	0.2110

surgery	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age	-.1491155	.0091827	-16.24	0.000	-.1671132	-.1311178
tum_size	-.0300775	.002898	-10.38	0.000	-.0357575	-.0243976
distant_mets	-2.102293	.2222609	-9.46	0.000	-2.537916	-1.666669
_cons	14.30809	.7609744	18.80	0.000	12.81661	15.79957

- Probability of surgery being WLE

We assumed that women receiving surgery could either be treated with WLE or mastectomy. Consequently, a regression model was constructed to estimate the likelihood of WLE given that the woman received surgery. The regression model was constructed only among women known to have

been treated with surgery and included age (in years), tumour size (in mm) and the presence of distant metastasis as covariates. The coefficient of the regression model was negative for age and tumour size indicating that the probability of surgery being WLE decreases as age and tumour size increase. Nevertheless, the regression's coefficient for distant metastasis was positive, indicating WLE was more likely to be performed compared to other type of surgery in the presence of distant metastasis.

The probability of mastectomy was calculated from the above.

Equation 4: logistic regression model to predict the probability of surgery being wide local excision

Logistic regression — Number of obs = 2082
LR chi2(3) = 231.74
Prob > chi2 = 0.0000
Log likelihood = -1327.0468 — Pseudo R2 = 0.0803

wle |	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0023957	.0084935	-0.28	0.778	-.0190427	.0142512
tum_size	-.0573701	.0044387	-12.93	0.000	-.0660697	-.0486704
distant_mets	.1334907	.3339516	0.40	0.689	-.5210424	.7880238
_cons	1.581254	.6581936	2.40	0.016	.2912182	2.87129

- Probability of radiotherapy

After obtaining clinical opinion and performing an exploratory analysis on the ECRIC dataset, the likelihood of radiotherapy was found to be different among women who have not been treated with surgery, women who have treated with WLE, and women receiving mastectomy. Therefore, three separate logistic regression models were constructed for each of the identified sub-groups. The estimated model only uses age as a covariate as this was believed to be the most relevant determinant for the decision to perform radiotherapy in addition to the type of surgery. In all the sub-groups, the regression coefficient for age was negative, indicating that age is inversely correlated with the probability of radiotherapy.

Equation 5: logistic regression model to predict the probability of radiotherapy among women who did not receive surgery

Logistic regression — Number of obs = 1168
LR chi2(1) = 83.41

Prob > chi2 = 0.0000

Log likelihood = -544.69934 Pseudo R2 = 0.0711

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1087436	.0126583	-8.59	0.000	-.1335535	-.0839338
_cons	7.429745	1.012724	7.34	0.000	5.444844	9.414647

Equation 6: logistic regression model to predict the probability of radiotherapy among women who received wide local excision

Logistic regression Number of obs = 1305

LR chi2(1) = 91.06

Prob > chi2 = 0.0000

Log likelihood = -631.68679 Pseudo R2 = 0.0672

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1117668	.011994	-9.32	0.000	-.1352746	-.088259
_cons	10.03281	.9491101	10.57	0.000	8.172587	11.89303

Equation 7: logistic regression model to predict the probability of radiotherapy among women who received mastectomy

Logistic regression Number of obs = 1350

LR chi2(1) = 19.71

Prob > chi2 = 0.0000

Log likelihood = -907.55672 Pseudo R2 = 0.0107

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0469548	.0107403	-4.37	0.000	-.0680055	-.0259042
_cons	3.294294	.8298219	3.97	0.000	1.667873	4.920715

- Probability of chemotherapy

Only a small proportion of elderly women in the ECRIC dataset were treated with chemotherapy. [2] A logistic regression model was constructed to estimate the likelihood of receiving chemotherapy using age only as covariate. This was believed to be the main determinant in the treatment decision in

older women. Age was found to be inversely correlated with the likelihood of receiving chemotherapy among elderly women (Equation 8).

Equation 8: logistic regression model to predict the probability of chemotherapy

Logistic regression	Number of obs	=	3757
	LR chi2(1)	=	60.52
	Prob > chi2	=	0.0000
Log likelihood = -480.4425	Pseudo R2	=	0.0593

chemotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1466639	.0216693	-6.77	0.000	-.1891348	-.1041929
_cons	7.779509	1.625621	4.79	0.000	4.593352	10.96567

- Probability of hormonal therapy

While only a small fraction of women were treated with chemotherapy, a large majority of women received hormonal therapy. After discussion with clinical opinion, a logistic regression model was constructed to estimate the likelihood of hormonal therapy using age and ER status as covariates (Equation 9). Age and tumour ER positivity were positively correlated with the probability of hormonal therapy, meaning that the probability increases as age increases and in women having ER^{+ive} tumours.

Equation 9: logistic regression model to predict the probability of hormonal therapy

Logistic regression	Number of obs	=	2080
	LR chi2(2)	=	392.10
	Prob > chi2	=	0.0000
Log likelihood = -700.34358	Pseudo R2	=	0.2187

hormone	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	.0202352	.011841	1.71	0.087	-.0029727	.0434432
_Ier_statu~3	2.843215	.1479378	19.22	0.000	2.553262	3.133168
_cons	-1.99883	.9342194	-2.14	0.032	-3.829866	-.1677932

- Probability of axillary sentinel node biopsy or sampling

Pre-analysis of the data showed a very different likelihood between women treated with WLE and women treated with mastectomy, with a very low probability among women treated with mastectomy. Clinical opinion indicated that the probability of SLNB or sampling would be similar whatever the type of surgery in clinical practice. There may be a tendency for more complete axillary dissection (ALND) in women undergoing mastectomy as this may have been mandated by a larger tumour size which correlates with node positivity. Consequently, a regression model was constructed only in women treated with WLE and applied to both women treated with WLE and mastectomy (Equation 10). The regression model included only age as a covariate. The regression's coefficient for age was negative, indicating that the probability of SLNB decreases as age increases.

Equation 10: logistic regression model to predict the probability of axxillary biopsy sampling among women receiving wide local excision

Logistic regression	Number of obs	=	1305
	LR chi2(1)	=	23.77
	Prob > chi2	=	0.0000
Log likelihood = -828.77775	Pseudo R2	=	0.0141

auxiliary_b~g	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0528274	.011137	-4.74	0.000	-.0746555	-.0309993
_cons	3.421105	.8553669	4.00	0.000	1.744616	5.097593

- Probability of axillary block dissection

Finally, we evaluated the probability associated with axillary block dissection (or ALND) in older women. Clinical opinion and pre-analysis of the data indicated that that the likelihood of ALND was different between women who have been treated with WLE and women who have been treated with mastectomy probably due to women with larger primary cancers having a greater likelihood of requiring mastectomy and also of having nodal disease (both are correlated with tumour size). Consequently, two separate regression models were constructed. Both models included age, the number of nodes positive (0, 1 – 3, >= 4) and having received SLNB. Age and SLNB were inversely correlated with the likelihood of ALND while a greater nodal involvement was associated with a greater probability of ALND as would be expected.

Equation 11: logistic regression model to predict the probability of auxiliary block dissection among women receiving wide local excision

Logistic regression — Number of obs = 849; LR chi2(4) = 775.47; Prob > chi2 = 0.0000; Log likelihood = -195.64064; Pseudo R2 = 0.6646

auxiliary_b~n	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0622697	.0287548	-2.17	0.030	-.1186282	-.0059113
_InodesG_1	.8188293	.3661105	2.24	0.025	.1012658	1.536393
_InodesG_2	.9852105	.5963994	1.65	0.099	-.1837108	2.154132
auxiliary_b~g	-5.646704	.3250771	-17.37	0.000	-6.283843	-5.009565
_cons	6.9675	2.216077	3.14	0.002	2.62407	11.31093

Equation 12: logistic regression model to predict the probability of axxillary block dissection among women mastectomy

Logistic regression — Number of obs = 1037; LR chi2(4) = 84.37; Prob > chi2 = 0.0000; Log likelihood = -518.83806; Pseudo R2 = 0.0752

auxilliry_b~n	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0263396	.0145816	-1.81	0.071	-.0549189	.0022397
_InodesG_1	.3845568	.1764802	2.18	0.029	.0386619	.7304517
_InodesG_2	1.073512	.2406881	4.46	0.000	.6017717	1.545252
auxiliary_b~g	-2.670834	.4112446	-6.49	0.000	-3.476859	-1.864809
_cons	3.078369	1.130585	2.72	0.006	.8624626	5.294276

Reference List

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2. ECRIC registry data. Data on file 2010.

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