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**Survival from primary breast cancer after routine clinical use of mammography. *The Breast Journal* , invited revision and resubmission.**

**Survival from Primary Breast Cancer After Routine Clinical Use of Mammography**

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**Running Title:** Survival from Primary Breast Cancer

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**ABSTRACT:** Clinical trials predominantly indicate that mammography provides a substantial breast cancer survival benefit; however, there is a need to demonstrate that this benefit extends to clinical practice, and the extent that current reductions in mortality are attributable to regular screening or adjuvant systemic therapy. Mammography was used routinely at our institution across a broad age range, in an era when most patients received no adjuvant systemic therapy.

We examined breast cancer survival for a cohort of 678 stage 1-3 primary invasive breast cancer patients accrued 1971-90, and followed to 1996; 18% received adjuvant hormonal therapy and 15%, adjuvant chemotherapy. There were 61 women <40; 136, 40-49; 341, 50-69; 140,  $\geq$ 70. Factors available for multivariate investigations were age (years), tumour size (cm), nodal status (N-,Nx,N+), ER (fmol/mg protein), PgR (fmol/mg protein), adjuvant radiotherapy (no,yes), adjuvant hormonal therapy (no,yes), and adjuvant chemotherapy (no,yes). Forward step-wise multivariate regression with log-normal survival analysis was used to examine the effects of these factors on disease-specific survival. Ten-year survival by tumour size was adjusted for the effects of other significant factors. For women <40 years of age, 10-year survival at the T1a, T1b, T1c and T2 cut-points for tumour size is respectively 0.77, 0.74, 0.67, 0.44; for 40-49, it is 0.92, 0.90, 0.85, 0.62; for 50-69, it is 0.81, 0.79, 0.75, 0.62; for  $\geq$ 70, it is 0.84, 0.81, 0.73, 0.44. With routine use of clinical mammography and up to 26 years of follow-up, we found breast cancer survival to be significantly better ( $p \leq 0.05$ ) for all women with smaller tumours and that survival indicated a change in natural disease history with early detection. The Canadian National Breast Screening Study (NBSS) **controls** had significantly smaller tumours ( $p < 0.001$ ) than our patients which may indicate access to mammography outside of the NBSS that reduced the apparent survival benefit for clinical trial mammography.

**Key Words:** breast cancer, mammography, survival, tumour size.

## **INTRODUCTION:**

Most clinical trials (1-4) have indicated that the regular utilization of screening mammography provides a substantial survival benefit for women 50-69; an exception is the Canadian National Breast Screening Study-2. (NBSS) which did not show a survival benefit with screening mammography, even after 13 years of follow-up (5). Regular screening for women 40-49 has been debated (6,7) since until recently (2-4,8), the demonstrated benefits in randomized clinical trials (1) had not been consistently as great as those for women 50-69. For women 40-74, in the Swedish Two County trial (4), cumulative mortality data from the time of randomization onward was used to illustrate that there is a reduction in mortality from early detection that is not an artifact of lead time or length bias. Meanwhile, women  $\geq 70$  years of age have frequently not been included in randomized clinical trials (9), although screening should perhaps be considered for this age group (10,11).

Many international screening programs focus on women 50-69. This is true for Canada (12,13), although a large amount of Canadian screening takes place outside of organized programs (12). Screening programs generally began after most clinical trials showed survival benefit, and the long natural history for early breast cancer may mean that it is too early in many instances to assess the efficacy of implementing screening at a population level.

Reports of large short term declines in breast cancer mortality in the United States (14), have been attributed in part to early detection (14,15); this early detection is at a localized stage where there is a 97% five-year relative survival (16). Detection at this stage is frequently possible only with mammography; additionally, a woman's risk of axillary lymph node involvement increases with tumour size (4). A 63% reduction in population-based mortality has recently been attributed to screening mammography as a result of wide-scale utilization of "service" mammography in Sweden (17). However, it is difficult to separate the potential confounding between the introduction of screening mammography and the concurrent movement towards more universal administration of adjuvant systemic therapy (14,17-19).

We have up to 26 years follow-up for a cohort of women who underwent screening (20-24), but usually did not receive adjuvant systemic therapy. At **Women's College Hospital (WCH)**, imaging radiologists and clinicians made a decision to routinely offer mammography in the mid-1960's based on early clinical trial evidence of its effectiveness. The offer of mammography was made to a broad age range of women, generally all those  $\geq 35$  years of age. Most patients in our cohort, accrued in the 1970's and 1980's, received no adjuvant systemic therapy (18% received adjuvant hormonal therapy; 15%, adjuvant chemotherapy). We now use this patient data to examine the embedded premise in clinical management decisions at our institution, that routine use of mammography is beneficial in improving survival from breast cancer for women in the age groups  $<40$ , 40-49, 50-69, and  $\geq 70$  years of age.

Further, our institution's policy for mammography made it ineligible to participate in the NBSS (5). We use our data to examine whether the lack of significant effect for mammography in the NBSS (5,25) may be due to the controls receiving mammography off study.

## **MATERIALS AND METHODS:**

### **Purpose**

1. To examine the premise that the routine use of mammography is beneficial in improving survival from breast cancer for women in the age groups  $<40$ , 40-49, 50-69, and  $\geq 70$  years of age:
  - a) We tested the hypothesis that it is not beneficial in any or all of the age groups, where survival attributable to mammographic detection is inferred by survival at tumour sizes usually detectable only by mammography and survival by tumour size is adjusted for the effects of other significant factors.
  - b) After finding significant differences in a), we examined whether improved survival may alter the natural disease history, by whether survival curves for patients with small tumours are just lateral shifts of perhaps a few years along the time axis to those for patients with large tumours.
2. To examine whether the lack of significant effect for mammography in the NBSS (5,25) may be due to the controls receiving mammography off study:

All of our patients received mammography so we tested the hypothesis that there are no differences in tumour sizes between our WCH patient group and i.) the NBSS case group who were scheduled for annual mammography and ii.) the NBSS control group who were not scheduled for study mammography. After the tests of 1., if the NBSS control group had similar tumour sizes to those detected with the known mammography utilization at WCH, then one might anticipate a reduction in treatment effect between NBSS cases and controls.

### **Patients**

With routine mammography at WCH since the mid-1960's, the imaging radiologists had established mammography expertise by the beginning of our study in 1971. In the cohort accrual period, women were generally offered a baseline mammogram around 35, with repeat mammography every 1-2 years, depending on the physician and patient; mammography was generally continued past 70. All the breast cancer patients assessed and followed were from the surgical practice of E.B. Fish, and all patients underwent mammography in conjunction with their initial surgical assessment. The women presented with unilateral primary invasive breast cancer, with no previous history of carcinoma, except possibly in situ cervix or non-melanoma skin (both of which would be expected to have minimal effects on survival). The cohort of 678 consecutive patients meeting these criteria were accrued between 1971 and 1990, and were updated to 1996. There was 90% complete follow-up; median follow-up for those alive was 8.4 years.

The pathologic tumour size, by microscopic examination, was available for all but 17 of the 678 patients. The accrual is cross-tabulated by tumour size ( $\leq 0.5$ , (0.5-1.0], (1.0-2.0], (2.0-5.0],  $> 5.0$  cm) and year of primary surgery (1971-75, 1976-80, 1981-85, 1986-90) (Table 1). There is an increase in number of cases accrued in the later five-year periods, but no evidence of a significant change in tumour sizes across the accrual period ( $p=0.65$ , by Pearson chi-square test).

### **Surgical Procedure**

In all, 366 patients received a lumpectomy; 119 were clinically node negative and elected to have no axillary dissection, while 247 had an axillary dissection (20). Lumpectomy is defined as

a surgical attempt to remove the entire tumour and enough surrounding tissue to ensure the excision was adequate. Usually, about 2 cm of normal breast tissue was removed in each direction, and nearly always, the underlying pectoralis fascia. If the tumour was near the skin, a thin ellipse of skin was taken to indicate the anterior margin. The specimens were inked and they were examined by a pathologist in gross at the time of surgery, and on paraffin sections to assess the borders. A mastectomy was performed on 312 patients (simple or subcutaneous, 50 patients; modified radical, 262 patients) (20).

In the NSABP-B04 clinical trial (26), a delayed axillary dissection did not substantially alter patient survival. This was the basis for the practice of offering a delayed axillary dissection, as required, to clinically node-negative elderly patients. Survival from breast cancer was similar for elderly patients who were pathologically and clinically node-negative (20), and we did not find that nodal status had an important multivariate influence on breast cancer death for the elderly. As the group of clinically node-negative (Nx) patients may contain some patients who are node positive, the factor nodal status was defined as (pathologically node negative, N-; clinically node negative, Nx; pathologically node positive, N+).

### **Adjuvant Therapy**

Currently lumpectomy would usually be followed with adjuvant radiotherapy; this was not the practice at our institution during the 1970's and 1980's (27). Some patients were entered into randomized trials designed to determine the benefit of radiation and drew the no-radiation arm, but most received no radiotherapy because of surgeon and patient preference. However, as stated above, lumpectomy for our study cohort involved wide excision with the usual removal of 2 cm of normal tissue. Adjuvant systemic therapy was also not standard during this period. Thus, the infrequent administration of single or multiple modalities of adjuvant therapy (radiotherapy (24%), hormonal therapy (18%), chemotherapy (15%)) with lumpectomy **or** mastectomy was determined by surgeon and patient preference, and may have been associated a priori with poorer prognosis.

### **Event of Interest**

The cause of death was ascertained by medical review of patient charts to be from breast cancer or other causes; the event of interest was death from breast cancer. A patient's time on study was the time from definitive surgery until death from breast cancer (event), time until death from another cause (patient was "censored" at time of death), or length of follow-up (patient was alive and well - "censored"). As previously reported (20), most women diagnosed with breast cancer before 65 years of age died from breast cancer while about 50% of the deaths for women 65 or older were from another cause. The majority of patients and breast cancer deaths are in age groups which experience few deaths from other causes. We investigated the effects of factors on time to breast cancer death (**disease-specific survival; DSS**).

### **Factors**

We investigated the (univariate; multivariate) effects of the factors age (<40,40-49,50-69,≥70; in years), pathologic microscopically determined tumour size (≤0.5, (0.5,1.0],[1.0,2.0],[2.0,5.0],>5.0 cm; cm), nodal status (N-,Nx,N+ - coded 0,1,2), **Estrogen and Progesterone Receptors** [both **ER** and **PgR** both <10,≥10 fmol/mg protein; fmol/mg protein, as  $\log(\text{ER} + 0.5)$  and  $\log(\text{PgR} + 0.5)$  (30)], adjuvant radiotherapy (no,yes), adjuvant hormonal therapy (no,yes), and adjuvant chemotherapy (no,yes).

### **Univariate analyses**

The breast cancer deaths over the study period are reported as estimates of the likelihood of death from breast cancer by factor subgroup (28). The univariate effects of the factors on survival from breast cancer were assessed with the Wilcoxon (Peto-Prentice) test statistic (29) and Kaplan-Meier plots were made for each investigational factor.

### **Multivariate analyses**

The process used in the multivariate analyses was i.) to determine which factors had a significant association with survival, ii.) to check the adequacy of the fit of the multivariate models across the full time span and range of tumour sizes, iii.) to produce age-specific survivor plots by tumour size, after adjusting for the effects of other significant factors, iv.) to report 10-year adjusted survival by age-group and tumour size.

i.) We investigated the multivariate effects of the factors on DSS for all ages and the four age groups <40, 40-49, 50-69, and  $\geq 70$  years of age, for which the general utilization of screening mammography may differ, particularly by country. For women under 40 years of age, screening is frequently reserved for those with a family history of breast cancer. Women in the 40-49 age group are not universally eligible for active recruitment to receive screening through organized screening programs. Women 50-69 are those targeted in most programs to receive regular mammographic screening. Meanwhile, women 70 and older again are not universally eligible for programmatic screening.

With the exception of nodal status where Nx patients are known to be clinically node negative, patients with missing data for any factor were not included in the multivariate analyses. Due to the large amount of missing data for PgR, analyses were performed both with and without PgR; the only results reported here are those without PgR since it was not included in the best models. The use of the smaller data set, obtained by including PgR, did not substantially alter the survival results by tumour size, for the four age groups.

Multivariate effects were assessed with step-wise forward regression using Cox and log-normal survival analyses (31), performed for the whole patient group and the four age groups. The model improvement for the addition of a factor to the model was assessed with the likelihood ratio criterion,  $-2\log R \sim \chi^2_{(1)}$  under the assumption that the factor is not associated with time to disease-specific death; R is the ratio of the likelihood for the model without a particular factor to that for the model with the factor. A factor was added if  $p \leq 0.05$ , and all factors maintained significance once they were included in the model. The same significant factors were indicated in these analyses with both Cox and log-normal model-types, but survivor plots with the log-normal model are smoother as they do not hinge on specific event times.

ii.) The results obtained with the log-normal model are reported here. This model choice is well-supported for breast cancer data (32). The underlying assumption for a log-normal model is that after a certain point in time the risk of breast cancer death, on for instance an annual basis, will decrease. It would be fairly well accepted from clinical practice that after 3, 5, or 10 years that

this does happen. We utilized Cox-Snell residual plots (33) to check the adequacy of the fit for the regression models, for each age group, and found that it was adequate across the full time span and tumour sizes.

iii.) We have included log-normal survivor plots here for up to 26 years follow-up to indicate survival by different tumour sizes; other factors included in the multivariate models are controlled for at mean values.

iv.) Further, we used log-normal survivor functions to obtain 10-year survival (close to median follow-up for those alive) by tumour size; the advantage is that survival is estimated for a particular patient's tumour size, i.e. for 1.0 cm instead of a range of tumour sizes, providing appropriate survival information corresponding to that needed for clinical decisions for an individual patient. Ten-year survival is reported for tumour sizes corresponding to clinical staging cut-points at 0.5 cm (T1a), 1.0 cm (T1b), 2.0 cm (T1c), and 5.0 cm (T2). The results are stratified by age group to emulate the eventual clinical application. It is important that there were tumours smaller than 0.5 cm for each age group, and that we had long enough follow-up that we were able to demonstrate adequacy of the models for patients who survived breast cancer for 10 years.

### **Comparisons of WCH and NBSS tumour sizes**

The sizes of breast cancer tumours found in women 40-59 who participated in the NBSS have been reported (34) by whether they were randomized to receive mammography. For women receiving trial mammography who had breast cancers detected, 42% of the tumours were T1a/T1b, 35% were T1c, 21% T2, and 2% T3/T4; the corresponding data for controls were 29%, 38%, 30% and 3%. We used Pearson chi-square tests to compare the sizes of tumours detected in our patients aged 40-59 with those observed in the NBSS.

### **RESULTS:**

Our univariate results for all ages of women were reported (20) previously, and are repeated with the kind permission of the original journal. Table 2 contains the test statistics for all the investigational factors, with greater refinement provided here for tumour size. Figure 1 is the

Kaplan-Meier plot for tumour size. Women had significantly better survival from breast cancer with smaller tumours ( $p < 0.001$ ), no axillary lymph node involvement ( $p < 0.001$ ), and tumours with higher ER ( $p = 0.002$ ) and PgR ( $p = 0.01$ ). For all ages of patients, the DSS with a tumour  $\leq 0.5$  cm was 30/33 (91%); with a tumour (0.5,1.0] cm, 68/79 (86%); with a tumour (1.0,2.0] cm, 204/252 (81%); with a tumour (2.0,5.0] cm, 189/265 (71%); and with a tumour  $> 5$  cm, 17/32 (53%) ( $p = 0.001$ ). Seventeen patients had unknown tumour size; 8/17 (47%) survived; 38% of patients surviving and 67% of those who died were node positive. The DSS by age group is 42/61 (69%) for women  $< 40$ ; 107/136 (79%) for those 40-49; 257/341 (75%) for those 50-69; and 110/140 (79%) for those  $\geq 70$  ( $p = 0.39$ ).

The multivariate log-normal models are given in Table 3; the model fits were adequate as residual plots did not indicate trends. A larger tumour size was associated with poorer DSS ( $p \leq 0.05$ , in all instances). For patients of all ages and patients 50-69, positive nodal status was associated with worse DSS, while higher ER was associated with better survival for women 40-49 and 50-69.

The 10-year survival by age group and at the clinical staging cut-points for tumour size are given in Table 4. In all instances, there was a significant improvement in survival for patients who had tumours detected when they were smaller: with a 0.5 cm tumour, the proportion surviving breast cancer ranged from 0.77-0.92; with a 1 cm tumour, 0.74-0.90; with a 2 cm tumour, 0.67-0.85; and with a 5 cm tumour, 0.44-0.62. Figures 2-5 show the survivor plots by age and tumour size, controlling for other factors in the multivariate models.

In the NBSS, women who developed breast cancer, both those who received trial mammography and those who were controls, had significantly smaller tumour sizes ( $p < 0.001$ ) than our patients. In the comparison between our patients and the NBSS controls, there were large  $\chi^2_{(1)}$  contributions for T1a/T1b, T2, and T3/T4 tumours. Seventeen percent of our patients 40-59 and 29% of the NBSS controls (35) had T1a/T1b tumours; 36% of our patients and 38% of the NBSS controls had T1c tumours; 41% of our patients and 30% of the NBSS controls had T2 tumours; 5% of our patients and 3% of the NBSS controls had T3/T4 tumours.

**DISCUSSION:**

Clinical trials have demonstrated sufficient benefit for mammographic screening for at least some ages of women so that broad population based screening is being implemented in many countries. The efficacy of such screening requires long term population based follow-up to ascertain that the indications from clinical trials are generalizable. There is a need for the equivalent of phase IV trials to ensure that population changes are correctly attributed. Current trends in breast cancer incidence and mortality have been assessed with the NCI Surveillance Epidemiology and End Results (SEER) database which covers a representative 14% sample of the US population and has good data quality control measures (35). Early reports of significant reductions in mortality from breast cancer have been attributed to early detection of breast tumours as well as improved chemotherapy (14,15). The full effect of treating tumours at the smaller sizes, usually only detectable with mammography, will require decades of follow-up for population cohorts who regularly undergo screening.

In a large pre-mammography cohort of French patients, it is noteworthy that the clinical tumour size exceeded 1 cm for all patients, with 88% of patients having tumours larger than 2.5 cm (36-39). Meanwhile, our institution's mammography series had 54% of the breast cancers detected with pathologic/microscopically determined T1 tumours ( $\leq 2$  cm in size); 17% of patients had T1a/T1b tumours ( $\leq 1$  cm). The quality of the mammography was such that we found similar proportions of small tumours throughout the accrual period. Our proportion of T1 tumours is comparable to more recent U.S. experience reported for the SEER data, where 60% of the tumours were diagnosed at a localized state (16).

Our patient cohort had up to 26 years of follow-up. We utilized the experience of this patient cohort to provide survival plots for different age groups at particular tumour sizes; these plots incorporate adjustment for the effects of other significant factors [i.e. ER (and nodal status)] for better attribution of the survival effect of tumour size. The range of sizes examined covers the spectrum from likely palpable (5 cm), usually palpable (2 cm), through frequently non-palpable (1 cm) and usually non-palpable (0.5 cm). In all instances, there was significantly longer survival

for patients with tumour sizes usually detectable only with mammography, as compared to sizes that would be clinically detectable. For the four age groups, the DSS ranged from 0.77-0.92 with a 0.5 cm tumour, 0.74-0.90 with a 1 cm tumour, 0.67-0.85 with a 2 cm tumour, and 0.44-0.62 with a 5 cm tumour.

The univariate survival plots (Figure 1) appear to be plateauing at different levels by tumour size. Meanwhile, the multivariate survival plots indicate an ever widening "lead time" survival advantage for patients with small tumours at long follow-up. These findings are reminiscent of the results of Tabar, et al. (4), and are consistent with early detection and intervention altering the natural history of the disease.

It is notable that there were significant effects on survival in the  $<50$  and  $\geq 70$  age groups. We had up to 26 years of clinical follow-up; similar results were recently reported for the Swedish clinical trial data with 16 years of follow-up (4). The recent updates of the UK and Edinburgh trials (2,3) after respectively 16 and 14 years of follow-up found no significant differences in survival benefit by whether a woman was screened before or after 50 years of age. Furthermore, Tabar, et al. (4) showed that the benefit for 40-49 year olds may be reduced by a longer screening interval, and recommended screening every 12-18 months to minimize tumour progression.

There is only one clinical trial which has continued to show no survival benefit for the utilization of screening mammography; the Canadian NBSS clinical trial recently indicated no benefit for women 50-59, after 13 years of follow-up (5). We used the NBSS published tumour size data (34) to examine one of the hypotheses advanced in the latest NBSS reports (5,25), namely that the NBSS controls might have accessed mammography outside of the trial.

Women were recruited to the NBSS in the second half of our patient accrual when there were no Canadian Breast Screening programs (12,13); however, mammographic screening was available through institutions such as ours. The NBSS controls had smaller tumours detected than patients at our centre who had access to good quality mammography for this time period, as well as breast cancer specialists for good clinical management (clinical examinations, surgery,

and pathologic work-up). While mammography accessible to the NBSS controls in the 1980's may have been superior to that utilized at our institution in the 1970's, we did not find significantly different tumour sizes across our twenty years of accrual ( $p=0.65$ ). It is likely that there were different age distributions between the NBSS controls and our patients within the broad 40-59 age category used for comparative purposes. Age imbalances might lead to differences in ability to detect tumours for those under or over 50 years of age at diagnosis; however, the heavier weighting of the NBSS controls towards proportionately more women under 50, than a general population of breast cancer patients, would not be expected to lead to the detection of more small tumours. The NBSS controls 40-49 were scheduled to have only an initial NBSS physical examination, followed by usual care (40). Major frequent utilization of outside mammography by NBSS controls would reduce the apparent effectiveness of the trial mammography (5,25). Our patient group had significantly larger tumour sizes than both the NBSS cases and controls. Some women in the NBSS likely benefitted from improved mammography available in the 1990's, and the NBSS cases were scheduled for annual mammography while many of the WCH women underwent mammography every two years. For whatever reason, the NBSS controls had smaller tumours than those detected at our institution which had experienced mammographers.

Long follow-up for a broad age range of women who routinely underwent mammographic screening at WCH has provided an opportunity to assess survival from small breast cancers detected in a clinical setting; most of these women did not receive adjuvant systemic therapy. Our results are reported by age group at the staging cut-points for tumour sizes (for T1a, T1b, T1c, T2 tumours), after adjustment for the effects of other factors which had a significant effect on survival. There were significant improvements in survival for all women ( $p \leq 0.05$ ) with the smaller tumours usually only detectable with mammography, and an indication that the natural history of breast cancer may be altered with early detection and treatment. Better breast cancer survival than that reported here would be anticipated with the more general administration of (improved) adjuvant systemic therapy. Further, current mammography is superior to that

available during our study period, and should lead to the detection of a greater proportion of T1a and T1b tumours. The wide-spread regular use of screening mammography should continue to reduce breast cancer mortality in the United States (14,15) and other countries. As well, the development of new imaging technology that incorporates a comprehensive biological interface may lead to future dramatic improvements in prognosis for breast cancer (41).

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TABLE 1. Tumour Size by Year of Primary Surgery

Tumour Size	Number of Patients (%)				All Years	P-value <sup>1</sup>
	1971-75	1976-80	1981-85	1986-90		
≤0.5 cm	1 (2.1%)	8 (7.1%)	8 (3.2%)	16 (6.3%)	33 (5.0%)	
(0.5,1.0] cm	6 (12.5%)	17 (15.0%)	26 (10.5%)	30 (11.9%)	79 (12.0%)	
(1.0,2.0] cm	16 (33.3%)	46 (40.7%)	97 (39.1%)	93 (36.9%)	252 (38.1%)	0.65
(2.0,5.0] cm	22 (45.8%)	37 (32.7%)	107 (43.1%)	99 (39.3%)	265 (40.1%)	
>5.0 cm	3 (6.2%)	5 (4.4%)	10 (4.0%)	14 (5.6%)	32 (4.8%)	
All Sizes	48	113	248	252	661	

<sup>1</sup> P-value based on Pearson chi-square test.

TABLE 2. Deaths from Breast Cancer by Factor Subgroup

Factor	Number of Cases	Deaths	P-value <sup>1</sup>
<b>Age</b>			
<40	61	19 (31%)	0.39
40-49	136	29 (21%)	
50-69	341	84 (25%)	
≥70	140	30 (21%)	
<b>Tumour size in cm</b>			
(# patients<40,40-49,50-69,≥70)			
≤0.5 cm (3,8,16,6)	33	3 (9%)	<0.001
(0.5,1.0] cm (7,14,42,16)	79	11 (14%)	
(1.0,2.0] cm (24,44,126,58)	252	48 (19%)	
(2.0,5.0] cm (25,56,134,50)	265	76 (29%)	
>5.0 cm (2,10,14,6)	32	15 (47%)	
Missing (0,4,9,4)	17	9 (53%)	
<b>Nodal Status</b>			
N-	251	42 (17%)	<0.001
Nx	169	30 (18%)	
N+	258	87 (34%)	
<b>ER</b>			
<10 fmol/mg protein	115	36 (31%)	0.002
≥10 fmol/mg protein	472	106 (22%)	
<b>PgR</b>			
<10 fmol/mg protein	90	24 (27%)	0.01
≥10 fmol/mg protein	353	73 (21%)	
<b>Adjuvant Radiation</b>			
no	517	128 (25%)	0.91
yes	159	31 (19%)	
<b>Adjuvant Hormones</b>			
no	556	131 (24%)	0.54
yes	118	28 (24%)	
<b>Adjuvant Chemotherapy</b>			
no	572	131 (23%)	0.26
yes	104	28 (27%)	

<sup>1</sup> Based on the Wilcoxon (Peto-Prentice) test statistic.  
Results for nodal status, ER, PgR, adjuvant radiotherapy, adjuvant hormonal therapy, and adjuvant chemotherapy are

reproduced with the kind permission of the Annals of  
Surgical Oncology (22).

TABLE 3. Log-normal Survival Models by Age Group

Factor	<sup>1</sup> (S.E.)	P-value
All Patients:		
Tumour size	-0.20 (0.04)	<0.001
Nodal status	-0.26 (0.08)	0.001
ER	0.14 (0.05)	0.005
Age <40:		
Tumour size	-0.20 (0.09)	0.02
Age 40-49:		
Tumour size	-0.34 (0.11)	0.001
ER	0.36 (0.17)	0.03
Age 50-69:		
Tumour size	-0.15 (0.06)	0.02
Nodal status	-0.26 (0.11)	0.02
ER	0.14 (0.07)	0.03
Age ≥70:		
Tumour size	-0.31 (0.10)	0.001

<sup>1</sup> A negative/positive sign indicates a negative/positive effect on mortality.

TABLE 4. 10-Year Breast Cancer Survival by Age and Tumour Size

Age at Diagnosis	10-Year Survival by Tumour Size <sup>1</sup>			
	0.5 cm	1.0 cm	2.0 cm	5.0 cm
<40 years	0.77	0.74	0.67	0.44
40-49 years	0.92	0.90	0.85	0.62
50-69 years	0.81	0.79	0.75	0.62
≥70 years	0.84	0.81	0.73	0.44

<sup>1</sup>As described in the Methods section, survival is determined from multivariate log-normal survival analyses, after adjusting where appropriate, for the effects of other significant prognostic factors. For each age group, there are patients with tumour sizes which span this range, and the fit of the models is adequate.

**Legends for Figures:**

**for Figure 1.** Kaplan-Meier survival plot by tumour size for all ages of women, reproduced with the kind permission of the Annals of Surgical Oncology (22).

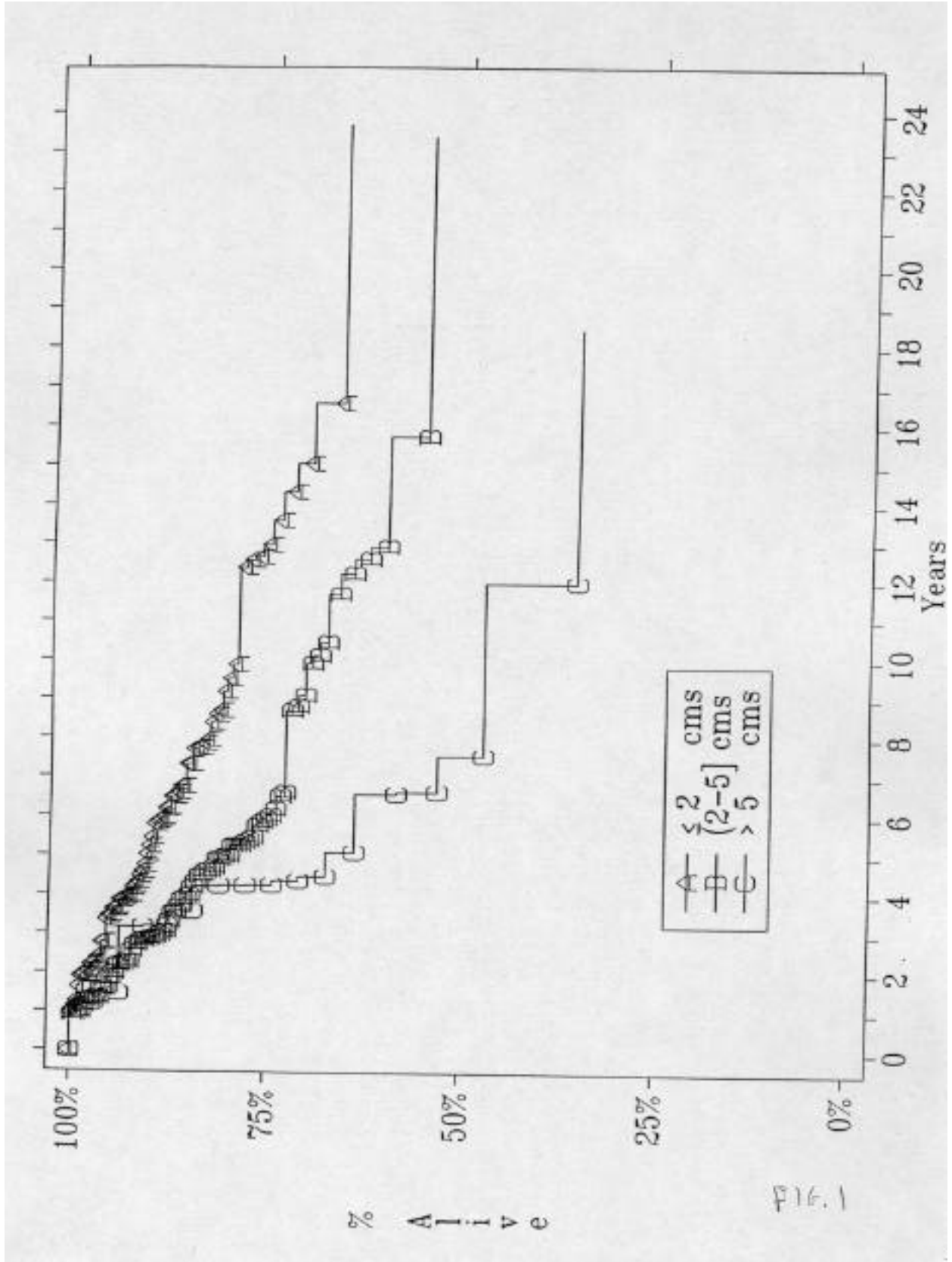
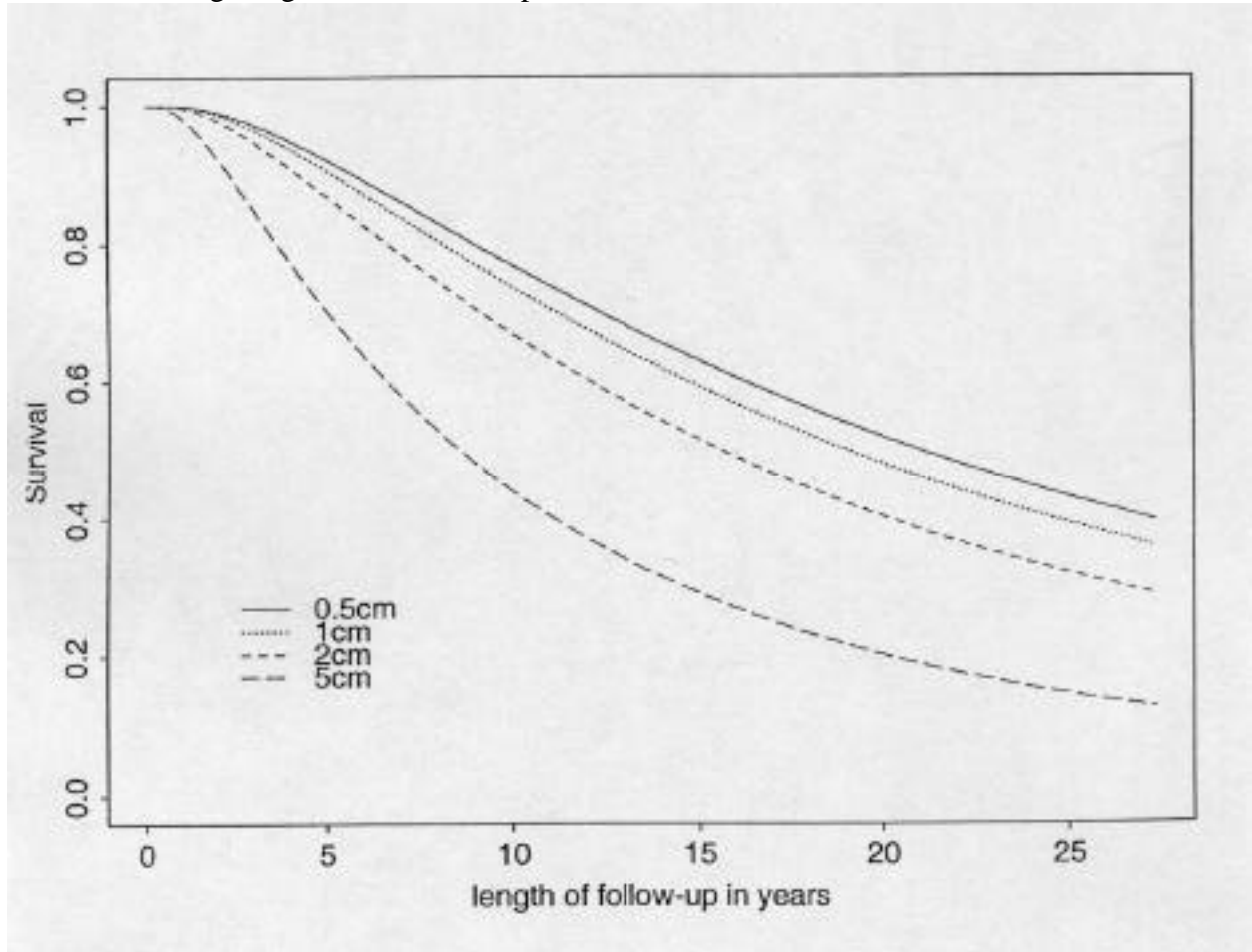
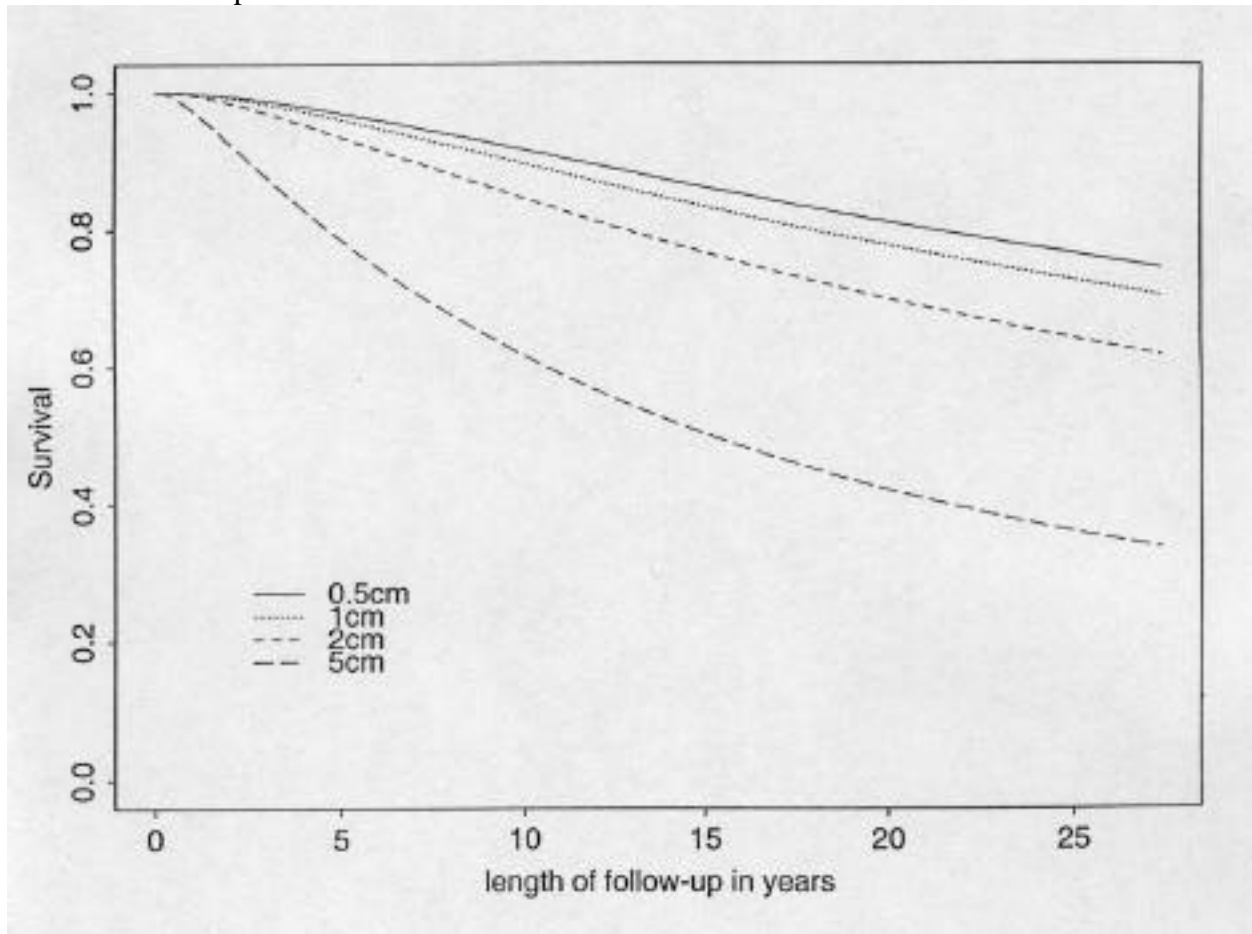


FIG. 1

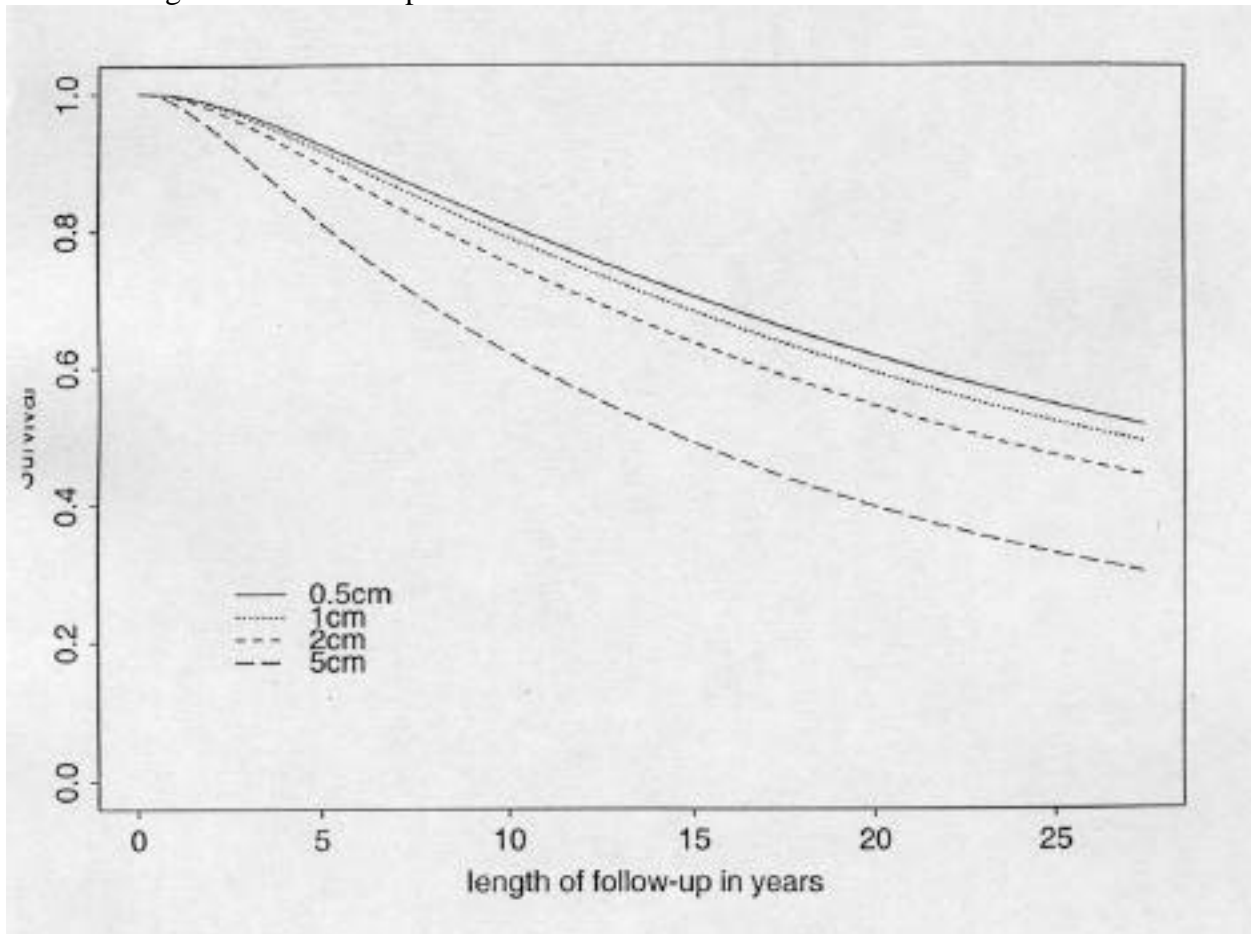
**for Figure 2.** Survival by tumour size for women aged <40 years, utilizing a log-normal survivor plot.



**for Figure 3.** Survival by tumour size for women aged 40-49 years, after adjusting for ER, utilizing a log-normal survivor plot.



**for Figure 4.** Survival by tumour size for women aged 50-69 years, after adjusting for nodal status and ER, utilizing a log-normal survivor plot.



**for Figure 5.** Survival by tumour size for women aged  $\geq 70$  years, utilizing a log-normal survivor plot.

