



**HAL**  
open science

## Factors influencing loco-regional relapse in older breast cancer patients treated with tumourectomy and tamoxifen

Michalis Kontos, Diane S. Allen, Hisham Hamed, Ian S. Fentiman

► **To cite this version:**

Michalis Kontos, Diane S. Allen, Hisham Hamed, Ian S. Fentiman. Factors influencing loco-regional relapse in older breast cancer patients treated with tumourectomy and tamoxifen. *EJSO - European Journal of Surgical Oncology*, 2011, 37 (12), pp.1051. 10.1016/j.ejso.2011.07.005 . hal-00750471

**HAL Id: hal-00750471**

**<https://hal.science/hal-00750471>**

Submitted on 10 Nov 2012

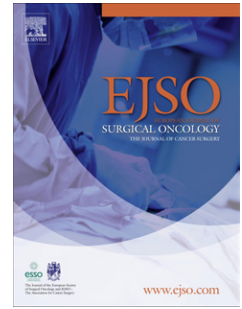
**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Accepted Manuscript

Title: Factors influencing loco-regional relapse in older breast cancer patients treated with tumourectomy and tamoxifen

Authors: Michalis Kontos, MD Diane S. Allen, MSc Hisham Hamed, PhD, FRCS Ian S. Fentiman, MD, DSc, FRCS



PII: S0748-7983(11)00390-8

DOI: [10.1016/j.ejso.2011.07.005](https://doi.org/10.1016/j.ejso.2011.07.005)

Reference: YEJSO 3197

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 25 July 2011

Please cite this article as: Kontos M, Allen DS, Hamed H, Fentiman IS. Factors influencing loco-regional relapse in older breast cancer patients treated with tumourectomy and tamoxifen, *European Journal of Surgical Oncology* (2011), doi: 10.1016/j.ejso.2011.07.005

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Factors influencing loco-regional relapse in older breast cancer patients treated with tumourectomy and tamoxifen.

**Michalis Kontos MD**

**Diane S Allen MSc**

**Hisham Hamed PhD FRCS**

**Ian S Fentiman MD DSc FRCS**

**Hedley Atkins Breast Unit**

**Guy's Hospital**

**London SE1 9RT**

**UK**

**Keywords: breast cancer, older patients, tamoxifen, loco-regional relapse, randomised trial**

**ABSTRACT**

**Background** In breast cancer patients ( $\geq 70$  years), tumourectomy plus tamoxifen (T + T) has a higher loco-regional relapse rate than mastectomy. This study examines factors influencing local recurrence in these cases.

**Methods** Clinical records of 71 patients aged  $\geq 70$  years, randomised to the T + T arm of a 2 randomised trials were reviewed. Cox Proportional Hazards model was used to determine the most significant variables.

**Results** After 15 years follow-up, loco-regional relapse occurred in 41%, of whom 5 had synchronous metastatic disease. Most tumours (67%), recurred in the index quadrant. Subsequently 21/24 patients with loco-regional recurrence only had salvage mastectomy. Three variables significantly predicted loco-regional recurrence: lympho-vascular invasion (HR [95% CI]: 11.88 [4.52, 31.22],  $p < 0.001$ ), ER negative status (HR [95% CI]: 3.61 [1.33, 9.79],  $p = 0.012$ ), and tumour necrosis (HR [95% CI]: 2.95 [1.13, 7.70],  $p = 0.027$ ). Final margin status was not associated with loco-regional relapse.

**Conclusions** Tumourectomy + Tamoxifen in older patients results in long term local control in the majority with most loco-regional failures being salvageable. Risk factors for local relapse are lymphovascular invasion, ER status and tumour necrosis. Negative tumour excision margins do not significantly change local outcome in the absence of radiotherapy. Lympho-vascular invasion significantly reduces survival time in these older patients.

## INTRODUCTION

As the population ages, women aged  $\geq 70$  are becoming an increasing proportion of breast cancer patients. In Europe and the US approximately 50% of all new breast cancers occur in women aged 70 years and older<sup>1 2</sup>. Because of misconceptions about age and co-morbidity, older women have been undertreated<sup>3 4</sup> and frequently omitted from clinical trials<sup>5</sup>, leading to a paucity of reliable data. Evidence from the relatively few randomised trials in older breast cancer patients is in support of surgery plus tamoxifen rather than tamoxifen alone<sup>6 7 8 9</sup>. Despite this, debate still exists about adequate extent of the surgery and the need for axillary surgery.

The EORTC 10850 trial has suggested the equivalence of tumourectomy plus tamoxifen (T + T) to modified radical mastectomy, in terms of overall survival<sup>9</sup>. Quality of life (QOL) analysis of these patients has reported fewer arm problems in the tumourectomy group and a shift in the direction of a benefit in body image<sup>10</sup>. On the other hand there were significantly more loco-regional relapses in the tumourectomy + tamoxifen group<sup>9</sup>.

The aim of present study was to review a series of breast cancer patients aged  $\geq 70$ , all receiving uniform treatment in the form of tumourectomy followed by tamoxifen and to ascertain the various clinico-pathological determinants of loco-regional relapse, and their effect on survival.

## PATIENTS AND METHODS

We reviewed the clinical files of all breast cancer patients aged  $\geq 70$  years, treated at the Breast Unit, Guy's Hospital, by tumourectomy and tamoxifen, as a part of randomised clinical trials (C

19 & C 28) between 1983 and 1990. Patients in C19 participated in a pilot trial conducted at Guy's Hospital, comparing modified radical mastectomy with T + T whereas those in C28 were the Guy's component of EORTC 10850. All patients had a histological diagnosis of operable breast cancer (T1 T2 T3a, N0 N1a N1b, M0). They all had a single primary with no evidence of Paget's disease of nipple. All had staging investigations (full blood count, biochemical screen, and chest x-ray) to rule out distant metastases.\*

Surgical treatment was tumourectomy followed by adjuvant tamoxifen 20 mg daily for the rest of their life or until development of relapse. Tamoxifen was given to all patients irrespective of estrogen receptor (ER) status as part of the protocol because, at the time of study design, it was thought that there was a benefit from tamoxifen in postmenopausal ER negative women. All patients were seen every 3 months for 2 years, then monthly for 3 years and thereafter annually. All patients were followed to death or for 15 years.

We recorded the pattern of relapse under two major categories, loco-regional and distant. Loco-regional recurrence was subdivided into breast recurrence in the index quadrant, breast recurrence elsewhere, breast multicentric recurrence and axillary relapse. Supraclavicular lymph node recurrence, contralateral breast recurrence, contralateral axillary metastasis and distant organ relapses were recorded as distant metastasis.

Patients who did and did not develop loco-regional relapse were compared for various *a priori* clinico-pathological factors using appropriate statistical measures. Factors examined to determine their influence on loco-regional relapse were patient age, clinical T size, clinical axillary nodal status, tumour type and grade, , presence of lympho-vascular invasion (LVI),

margin status, ER and PR status, presence of tumour necrosis, and area of the breast involved. The tumour was considered ER positive if containing >10femtomoles/mg cytosol protein.

### **Statistical analysis**

Univariate analyses were performed using chi-squared tests to determine statistical significance. A multivariate analysis using Cox Proportional Hazards was used to determine independent predicting factors of loco-regional recurrence. Kaplan-Meier plots were used for calculating loco-regional relapse free survival and overall survival. All statistical analyses were performed using SPSS v.16.0.

### **RESULTS**

In trials C 19 and C 28, patients aged  $\geq 70$  who agreed to participate were randomised to be treated with either T + T or modified radical mastectomy. There was a total of 79 patients on the T + T arm treated at Guy's Hospital between 1983 and 1990, but we were only able to review the full clinical records of 71 cases. Patient age at entry varied between 70 and 84 years with mean age 74.8 yrs. The majority of tumours were invasive ductal cancers (IDC) (77%) and ER positive (78%). In this study a positive margin was defined as the presence of invasive tumour at the surgical margins. The margin was described as close, when tumour was within 2 mm of surgical margin. Re-excision was not routinely performed for close or focally positive margins. In 34% of cases, margins were positive and in a further 30% the margins were close. The majority of tumours were T1/T2 and 27% of patients had one or more palpable axillary lymph

nodes at the time of first presentations. Out of 19 patients with clinically palpable nodes only 10 patients manifested relapse.

Table 1 shows the pattern of first relapse and subsequent outcome. Twenty-nine patients (41%) had a loco-regional relapse, of whom 5 had synchronous metastatic disease. Of the loco-regional recurrences 16 (67%) were in the index quadrant. After loco-regional relapse without distant metastases 21 out of 24 patients (88%) were salvaged by mastectomy and 8 remained disease-free for rest of their lives (38% of those salvaged, 33% of those with loco-regional relapse only).

Table 2 shows the distribution of the clinico-pathologic variables, and univariate analysis of their association with loco-regional recurrence. Factors found to be associated with development of loco-regional recurrence were the presence of lympho-vascular invasion ( $p=0.003$ ), higher grade tumours ( $p=0.028$ ), larger clinical tumour size ( $p=0.043$ ), negative ER status ( $p=0.045$ ) and the presence of tumour necrosis ( $p=0.048$ ). Age at diagnosis, clinical nodal status, PR status, site in breast and final margin status were not found to be associated with loco-regional relapse in these elderly patients.

To determine the most significant predictors of loco-regional relapse within 15 years of initial treatment, multivariable analysis was performed using the Cox Proportional Hazards model. The following variables were entered into the model using the backward stepwise method. Three variables were found to be significant predictors of loco-regional recurrence (Table 3). The most significant was the presence of lympho-vascular invasion (HR [95% CI]: 11.88 [4.52, 31.22],  $p<0.001$ ), ER negative status (HR [95% CI]: 3.61 [1.33, 9.79],  $p=0.012$ ), and the presence of tumour necrosis (HR [95% CI]: 2.95 [1.13, 7.70],  $p=0.027$ ).



Figure 1 shows loco-regional relapse free survival for each of these three significant predictors of loco-regional relapse. As expected, even by univariate analysis, all show significant differences in loco-regional relapse-free survival. Figure 2 shows overall survival for each of the significant predictors of loco-regional recurrence. The presence of lympho-vascular invasion significantly reduces survival time in these elderly patients ( $p=0.012$ ). Although not statistically significant at 15 years, ER negative patients appear to have reduced survival during the first 10 years after diagnosis. A similar result is found for those with tumour necrosis.

## DISCUSSION

Recent results from the EORTC 10850 trial have suggested that the preferred treatment option by older patients with breast cancer is T + T<sup>8</sup>. When compared with mastectomy T + T achieved superior body image and quality of life and similar overall survival<sup>8,9</sup>. The downside of this limited surgery without radiotherapy is worse local control, but without any survival disadvantage. The high incidence (41%) of loco-regional failure in this study is similar to the breast recurrence rate of 40% in NSABP B-06 trial when breast conservation was used without radiotherapy<sup>11</sup>. Interestingly long-term results from the Nottingham Trial comparing tamoxifen alone and subtotal mastectomy reported that 70% of those given tamoxifen alone relapsed<sup>12</sup>. This underlines the need for tumourectomy in combination with endocrine therapy. In this study we found that in 67% of cases, local recurrence has occurred in the index quadrant. In the remaining 33% of cases, recurrence was multicentric. Out of the 24 loco-regional failures without distant recurrence, 21 (88%) patients were salvaged by second surgery and 8 remained disease free for the rest of their lives. This supports the notion that in older patients, loco-regional relapse is not inevitably fatal and should be treated by surgery<sup>13 14</sup>.

Estrogen receptor positivity increases with advancing age<sup>15</sup>. In our study 78 % of tumours were ER positive. In contrast only 49% of cancers were PR positive. Similar high ER positivity (73.4%) and relatively low PR positivity (57%) associated with age >75 are also reported by Rhodes et al<sup>15</sup>. In this study all patients received tamoxifen irrespective of their ER status as a part of the protocol. Some studies have shown ER status as a strong predictor of local relapse in general breast cancer population<sup>16</sup>, concurring with our finding in this study of older patients, (ER-ve 34% and ER+ve 66%,  $p = 0.045$ ).

Lymphatic and vascular invasion suggest the possibility of local spread of tumour cells beyond gross margins and hence is considered as one of the predictors of loco-regional recurrence<sup>17</sup>. In this study no attempt was made to differentiate between blood vessel and lymphatic invasion. When invasion was recorded without separation into these categories, an incidence of 22% was found. Pinder et al have documented incidence of LVI between 23% and 57% in all ages (Pinder et al, 1994)<sup>18</sup>. The incidence of vascular invasion falls with increasing age<sup>19</sup>. In this study the presence of LVI has shown strongest association with loco-regional relapse ( $p=0.003$ ). If only breast recurrences are considered, the association is even stronger ( $p=0.0001$ ). Multivariate analysis has shown 3 variables that are independent predictors of loco-regional relapse: presence of LVI ( $p<0.001$ ), ER-ve tumour ( $p=0.012$ ) and presence of tumour necrosis ( $p=0.027$ ).

Age of the patient did not influence the local relapse rate ( $p = 1.00$ ). Preoperative clinical assessment of axillary nodal status was poorly associated with axillary recurrence ( $p= 0.932$ ). Out of 19 clinically node positive patients, 10 patients never manifested any recurrence in spite of no axillary treatment, reinforcing the inaccuracy of clinical assessment if used alone to determine nodal involvement. Location (quadrant) of the primary tumour did not show a significant influence on loco-regional relapse( $p=0.078$  ). Though IDC remained the most frequent histological type, 21% of the cancers were infiltrating lobular lesions and this high incidence in the older age groups has been reported by other workers<sup>19 20</sup> .

Definition of an adequate margin of resection and its influence on local relapse rate has always remained matter of debate with no consensus<sup>21 22</sup>. In this series of patients no special attempt was made to obtain radical margins, thus leaving around two thirds of patients with either close or focally positive margins. Statistical analysis suggests that there was no significant difference in local relapse rate among margin positive and margin negative patients ( $p=0.114$ ). This could

be interpreted as, in absence of radiotherapy cover, negative margins do not improve local control or alternatively that tamoxifen destroys residual ER+ve tumour cells. This observation is in agreement with previous reports which have demonstrated the need for local radiotherapy irrespective of extent of local surgery<sup>23 24</sup>.

A recent study has shown the safety of radiotherapy in patients above age 75 years and hence age alone should not be a reason for denial of post-lumpectomy breast irradiation<sup>25</sup>. The new technique of intra-operative radiotherapy (IORT) can be an alternative in older patients<sup>26 27</sup>. In the TARGIT-A trial, comparing a single dose of targeted intraoperative radiotherapy with a course of post-operative external radiotherapy, there were similar rates of local relapse in both arms with reduced morbidity in those treated intraoperatively<sup>27</sup>.

As a result of randomised trials demonstrating the superiority of aromatase inhibitors to tamoxifen as adjuvant treatment in post-menopausal women<sup>28 29 30</sup>, the role of tamoxifen in older women will be increasingly questioned. There is however a downside to the superior anti-estrogenic properties of aromatase inhibitors in that they increase bone loss and are associated with musculo-skeletal symptoms in up to 30% of cases. In a recent study, 29% of patients discontinued letrozole because of severe joint pain<sup>31</sup>. This may be a particular problem in older women with a pre-existing burden of osteopenia, osteoporosis and osteoarthritis. Through its partial estrogen agonist effect tamoxifen acts as an osteoprotective agent<sup>32</sup>, thereby obviating the need for use of bisphosphonates. Hence, after tumourectomy, tamoxifen may yet again play a role in the management of ER positive breast cancer in older women.

Word Count: 3021

Abstract = 302

Article without figures and references = 2107

ACCEPTED MANUSCRIPT

**Table 1 Pattern of first relapse and subsequent outcome**

Type of first relapse	No. patients	No. salvaged	Disease-free at last follow-up or at death
<b>No relapse</b>	<b>40 (56.3%)</b>		<b>40</b>
<b>Loco-regional</b>	<b>24 (33.8%)</b>		
<u>Breast</u>	<u>18</u>		
index quadrant	16	14	6
multicentric	2	2	2
<u>Axilla</u>	<u>2</u>	2	2
<u>Breast and axilla</u>	<u>4</u>	3	0
<b>Distant</b>	<b>6 (8.5%)</b>		
<u>Only distant</u>	<u>1</u>		
<u>Distant and local</u>	<u>5</u>		
<b>Opposite breast</b>	<b>1 (1.4%)</b>	1	1
<b>TOTAL</b>	<b>71 (100%)</b>		<b>51 (71.8%)</b>

**Table 2** The distribution of clinico-pathologic variables and their univariate association with loco-regional recurrence to 15 years.

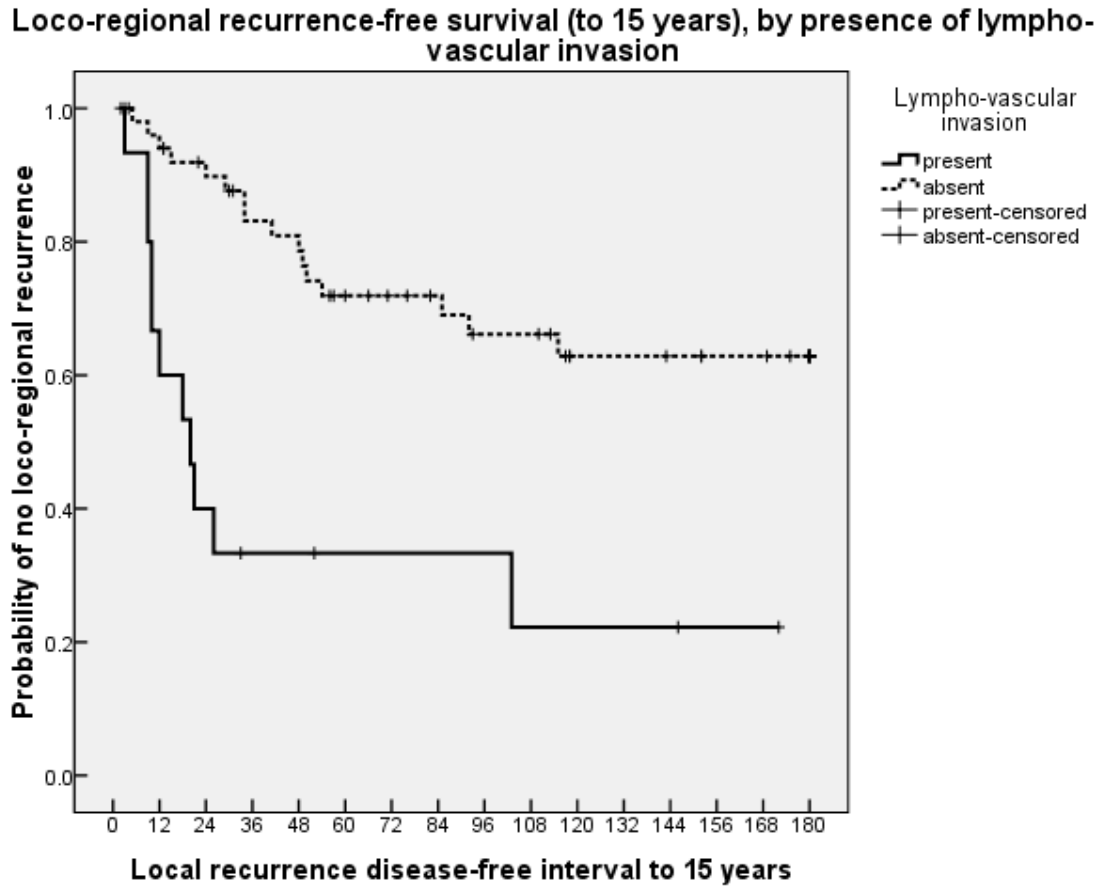
Variable	N (%)	No loco-regional recurrence	Loco-regional recurrence	Association Chi-square
<u>Age at diagnosis</u>				
70-74	39 (55%)	23 (55%)	16 (55%)	<i>p=0.978</i>
75-79	24 (34%)	14 (33%)	10 (35%)	
80+	8 (11%)	5 (12%)	3 (10%)	
<u>Clinical tumour size</u>				
T1	15 (21%)	13 (31%)	2 (7%)	<i>p=0.043</i>
T2	51 (72%)	27 (64%)	24 (83%)	
T3	5 (7%)	2 (5%)	3 (10%)	
<u>Clinical nodes</u>				
negative	52 (73%)	32 (76%)	20 (69%)	<i>p=0.499</i>
positive	19 (27%)	10 (24%)	9 (31%)	
<u>Tumour type/grade</u>				
I Duct Grade I	5 (7%)	5 (12%)	0	<i>p=0.028</i>
I Duct Grade II & I Lob	43 (63%)	28 (68%)	15 (56%)	
I Duct Grade III	20 (29%)	8 (20%)	12 (44%)	
not known	3			
<u>ER status</u>				
positive	55 (78%)	36 (86%)	19 (66%)	<i>p=0.045</i>
negative	16 (22%)	6 (14%)	10 (34%)	
<u>PR status</u>				
positive	35 (49%)	23 (55%)	12 (41%)	<i>p=0.268</i>
negative	36 (51%)	19 (45%)	17 (59%)	
<u>Tumour necrosis</u>				
absent	42 (62%)	28 (72%)	14 (48%)	<i>p=0.048</i>
present	26 (38%)	11 (28%)	15 (52%)	
not known	3			
<u>Lympho-vascular invasion</u>				
absent	53 (78%)	37 (90%)	16 (59%)	<i>p=0.003</i>
present	15 (22%)	4 (10%)	11 (41%)	
not known	3			
<u>Final margin status</u>				
clear	25 (36%)	19 (45%)	6 (22%)	<i>p=0.114</i>
close	21 (30%)	10 (24%)	11 (39%)	
positive	24 (34%)	13 (31%)	11 (39%)	
not known	1			
<u>Quadrant/area of breast</u>				
outer	43 (60%)	30 (71%)	13 (45%)	<i>p=0.078</i>
inner	19 (27%)	8 (19%)	11 (38%)	
central	9 (13%)	4 (10%)	5 (17%)	

**Table 3** Cox proportional hazards ratios for predictors of loco-regional recurrence. (62/71 used for analysis, 9 excluded for missing values)

Variable	All variables entered into the model	Significant predictors using backward conditional method
<u>Age at diagnosis</u>	<i>p=0.999</i>	
70-74	1.00	
75-79	1.01 (0.34, 3.03)	
80+	1.04 (0.22, 4.96)	
<u>Clinical tumour size</u>	<i>p=0.419</i>	
T1	1.00	
T2	2.23 (0.35, 14.10)	
T3	0.85 (0.11, 6.77)	
<u>Clinical nodes</u>	<i>p=0.932</i>	
negative	1.00	
positive	0.95 (0.29, 3.07)	
<u>Tumour type/grade</u>	<i>p=0.346</i>	
I Duct Grade I/II & I Lob	1.00	
I Duct Grade III	1.86 (0.51, 6.77)	
<u>ER status</u>	<i>p=0.172</i>	<b><i>p=0.012</i></b>
positive	1.00	1.00
negative	2.79 (0.64, 12.16)	3.61 (1.33, 9.79)
<u>PR status</u>	<i>p=0.771</i>	
positive	1.00	
negative	0.84 (0.26, 2.68)	
<u>Tumour necrosis</u>	<b><i>p=0.030</i></b>	<b><i>p=0.027</i></b>
absent	1.00	1.00
present	3.68 (1.14, 11.91)	2.95 (1.13, 7.70)
<u>Lympho-vascular invasion</u>	<b><i>p&lt;0.001</i></b>	<b><i>p&lt;0.001</i></b>
absent	1.00	1.00
present	12.53 (3.90, 40.21)	11.88 (4.52, 31.22)
<u>Final margin status</u>	<i>p=0.357</i>	
clear	1.00	
close	1.29 (0.41, 4.06)	
positive	2.42 (0.67, 8.82)	
<u>Quadrant/area of breast</u>	<i>p=0.213</i>	
outer	1.00	
inner	2.15 (0.71, 6.51)	
central	3.19 (0.72, 14.09)	



**Figure Ia. Local recurrence-free survival after T + T in elderly patients**

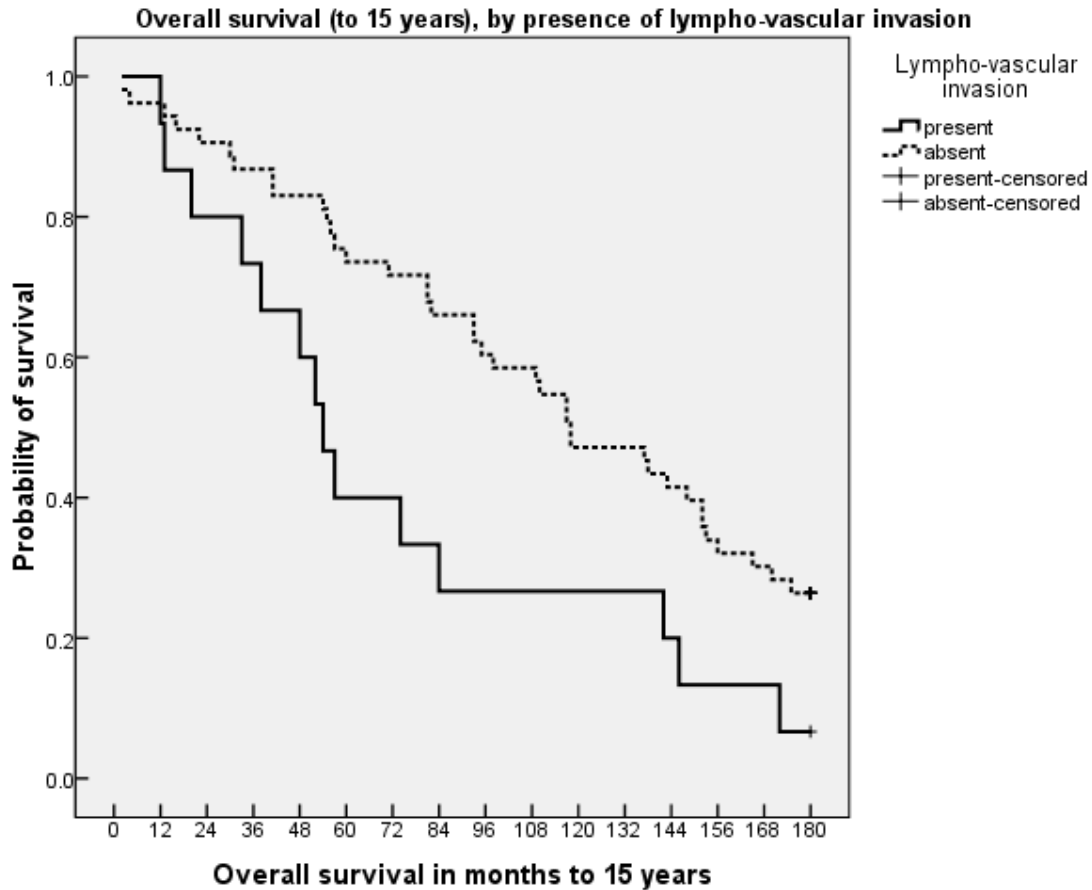


**Overall Comparisons**

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	15.246	1	.000

Test of equality of survival distributions for the different levels of Lympho-vascular invasion.

**Figure2a. Overall survival to 15 years by significant predictors of loco-regional recurrence.**

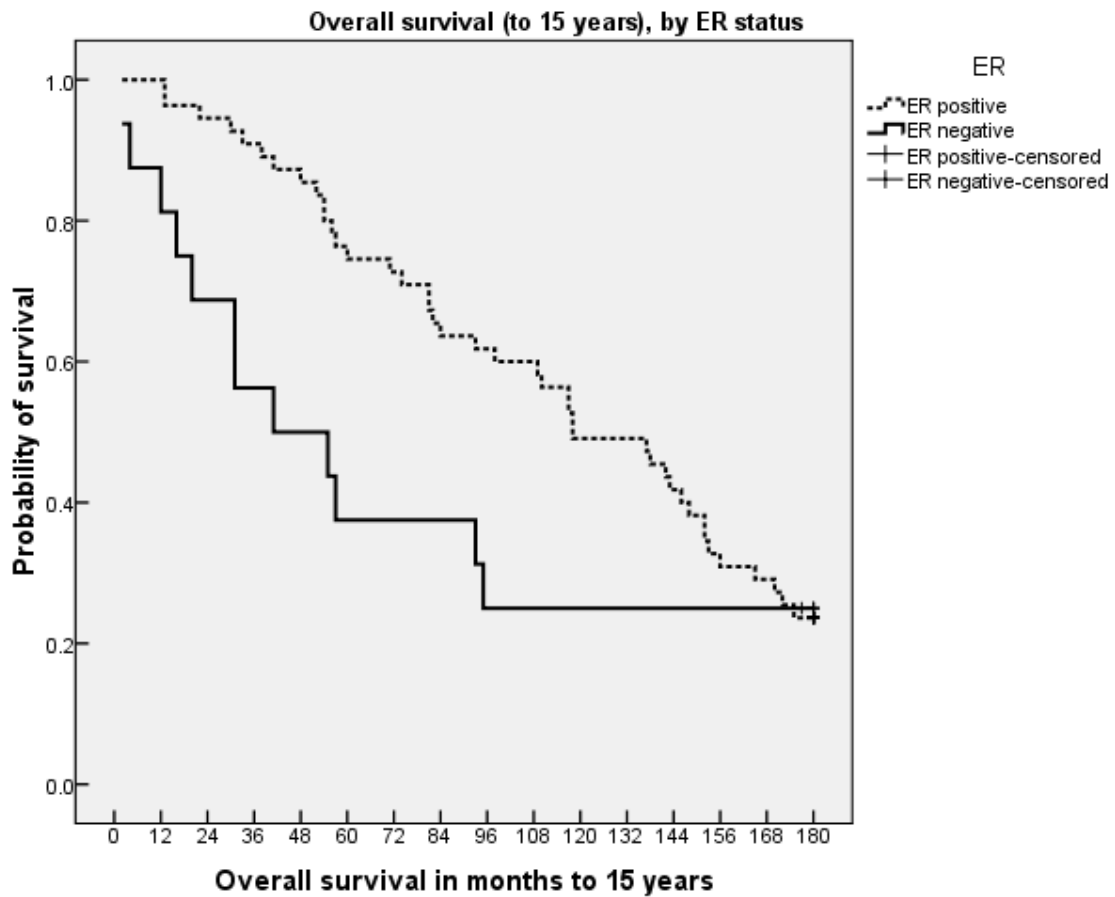


**Overall Comparisons**

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.269	1	.012

Test of equality of survival distributions for the different levels of Lympho-vascular invasion.

Figure 2b.

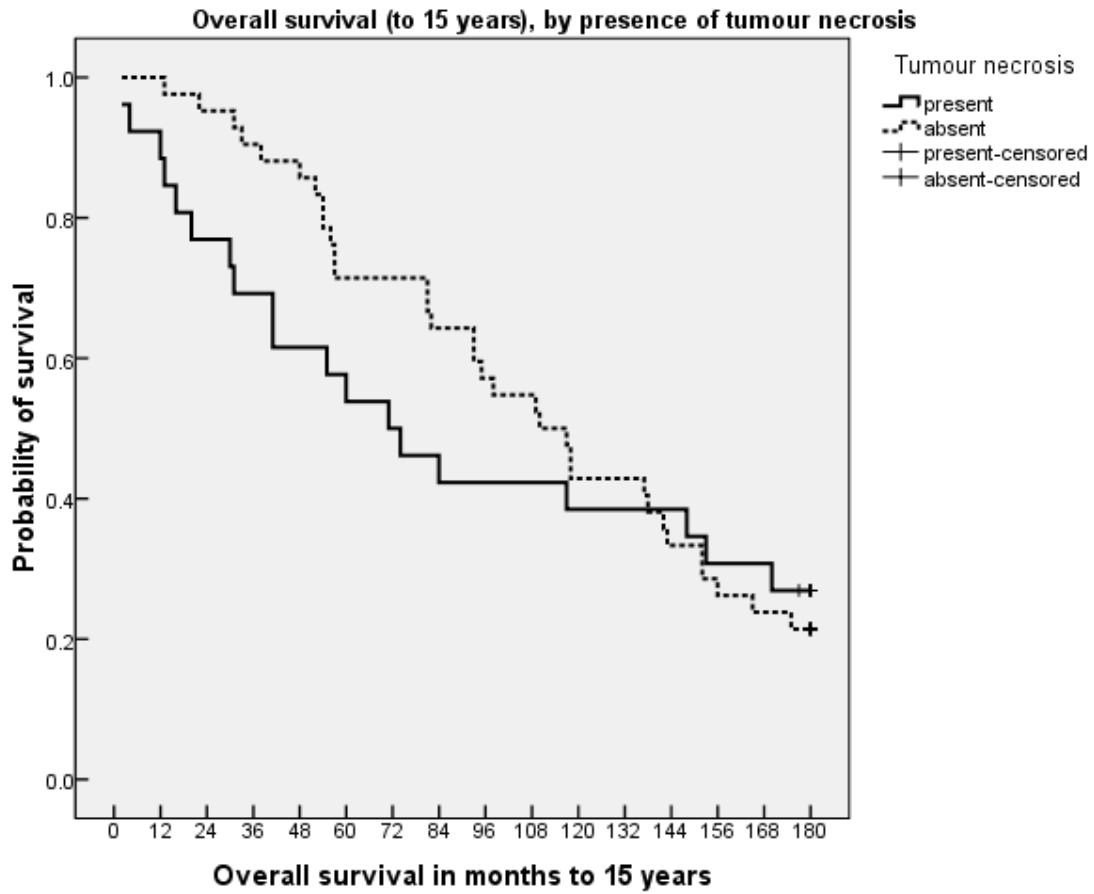


Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.893	1	.169

Test of equality of survival distributions for the different levels of ER.

Figure 2c.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.128	1	.720

Test of equality of survival distributions for the different levels of Tumour necrosis.

## References

- <sup>1</sup> Møller Jensen O, Estève J, Møller H, & Renard H. Cancer in the European Community and its Member States. *Eur J Cancer* 1990; **26**:1167- 1256.
- <sup>2</sup> Chu KC, Tarone RE, Kessler LG et al: Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *J Natl Cancer Inst* 1996; **88**:1571-1579.
- <sup>3</sup> Samet J, Hunt WC, Key C, et al. Choice of cancer treatment varies with age of patient. *JAMA*, 1986; **255**: 1302-7.
- <sup>4</sup> Ballard-Barbash R, Potosky AL, Harlan LC, Nayfield SG, Kessle LG. Factors Associated With Surgical and Radiation Therapy for Early Stage Breast Cancer in Older Women. *J Natl Cancer Inst.* 1996 ;**88**: 716-726.
- <sup>5</sup> Kemeny MM, Peterson BL, Kornblith AB, Cohen HJ et al: Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol* 2003; **21**:2268-2275.
- <sup>6</sup> Gazet JC, Ford HT, Coombes RC, Lowndes S et al: Prospective randomized trial of tamoxifen vs surgery in older patients with breast cancer. *Eur J Surg Oncol* 1996; **20**:207-214.
- <sup>7</sup> Fennessy M, Bates T, Macrae K, et al. Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 years with operable breast cancer. *Br J Surg.* 2004 ;**91**:699-704.
- <sup>8</sup> Robertson JF, Ellis IO, Elston CW, Blamey RW et al: Mastectomy or tamoxifen as initial therapy for operable breast cancer in older patients: 5-year follow-up. *Eur J Cancer* 1992; **28**: 908-910.
- <sup>9</sup> Fentiman I.S, van Zijl J, Karydas I, Chaudary A, Margreiter R, Legrande C, P. Therasse P. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. *Eur J Cancer* 2003; **39** :300–308
- <sup>10</sup> De Haes J.C.J.M, Curran D, Aaronson NK, Fentiman IS, On behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group (BCCG). Quality of life in breast cancer patients aged over 70 years, participating in the EORTC 10850 randomised clinical trial. *Eur J Cancer.* 2003 ; **39**: 945–951.
- <sup>11</sup> Fisher B, Redmond C. Lumpectomy for breast cancer: an update of the NSABP experience. National Surgical Adjuvant Breast and Bowel Project. *J Natl Cancer Inst Monogr* 1992; **11**: 7-13.
- <sup>12</sup> Chakrabarti J, Kenny FS, Syed BM, Robertson JFR, Blamey RW, Cheung KL. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer—Final results at 20-year follow-up. *Crit Rev Oncol/Hematol* (2010), doi:10.1016/j.critrevonc.2010.04.006

- <sup>13</sup> Halverson KJ, Perez CA, Kuske RR, Fineberg B et al. Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 1992; **23**: 285-291.
- <sup>14</sup> Kamby C, Sengelov L: Survival and pattern of failure following locoregional recurrence of breast cancer. *Clin Oncol (R Coll Radiol)* 1999; **11**: 156-163.
- <sup>15</sup> Rhodes A, Jasani B, Miller KD et al: Frequency of estrogen and progesterone receptor positivity by immunohistochemical analysis in 7016 breast carcinomas: correlation with patient age, assay sensitivity, threshold value, and mammographic screening. *J Clin Pathol* 2000; **53**: 688-696. .
- <sup>16</sup> Yaghan R, Stanton PD, Robertson KW, McArdle CS et al: Estrogen receptor status predicts local recurrence following breast conservation surgery for early breast cancer. *Eur J Surg Oncol* 1998; **24**: 424-426.
- <sup>17</sup> Wallgren A, Bonetti M, Gelber RD, Collins J: International Breast Cancer Study Group Trials I through VII. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 2003; **21**: 1205-1213.
- <sup>18</sup> Pinder SE, Ellis IO, Galea M, O'Rourke S, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship with recurrence and survival in a large study with long-term follow-up. *Histopathology*. 1994 ;**24**:41-7.
- <sup>19</sup> Fisher CJ, Egan MK, Smith P, Fentiman IS et al. Histopathology of breast cancer in relation to age. *Br J Cancer* 1997; **75**: 593-596.
- <sup>20</sup> Rosen PP, Lesser ML, Kinne DW : Breast carcinoma in extremes of age: a comparison of patients younger than 35 years and older than 75 years. *J Surg Oncol* 1985; **28**: 90-96.
- <sup>21</sup> Singletary SE: Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg* 2002; **184**: 383-93.
- <sup>22</sup> Assersohn L, Potts TJ, Ashley S, Nash AG, Naziri N: Local relapse in primary breast cancer patients with unexcised positive surgical margins after lumpectomy, radiotherapy and chemoendocrine therapy. *Ann Oncol*. 1999; **10**: 1451-1455.
- <sup>23</sup> Veronesi U, Salvadori B, Rilke F et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer* 1995; **31**: 1574-1579.
- <sup>24</sup> Shin E, Takatsuka Y, Okamura Y, Kikkawa N et al: A Retrospective Study of Breast Cancer Patients Treated with Quadrantectomy without Radiation Therapy. *Breast Cancer* 1999; **25**:109-116.
- <sup>25</sup> Deutsch M: Radiotherapy after lumpectomy for breast cancer in very old women. *Am J Clin Oncol* 2002; **25**: 48-49.

- 
- <sup>26</sup> Veronesi U, Orecchia R, Luini A et al: preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 2001; **37**: 2178-2183.
- <sup>27</sup> Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010; **376**: 91–102.
- <sup>28</sup> Baum M, Buzdar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;; **359**: 2131-2139.
- <sup>29</sup> Coombes RC, Hall E, Gibson LJ, et al. A randomised trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350**: 1081-1092.
- <sup>30</sup> Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97**: 1262-1271.
- <sup>31</sup> Briot K, Tubiana-Hulin M, Bastit L, Kloos I, Roux C. Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study. *Breast Cancer Res Treat* 2010; **120**: 127-134.
- <sup>32</sup> Fentiman IS, Saad Z, Chaudary MA, Fogelman I. Tamoxifen protects against steroid induced bone loss. *Eur J Cancer* 1992; **28**: 684-685.