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The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy

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Abstract

The aim of the study was to evaluate the importance of young age with regard to local control in a prospective cohort of 1085 women with pathological T1 tumours treated with breast conservative treatment (BCT). Patients were divided into two age groups: 40 years or younger, 7.8%, and older than 40 years, 92.2%. With a median follow-up of 71 months, the local recurrence rate was 10.6% in women $\leqslant 40$ years, and 3.7% in older women. The local recurrence-free survival (LRFS) was significantly different for the two age groups, respectively 89%, $\leqslant 40$ years, and 97.6%, >40 years ($P=0.0046$). A separate analysis showed a significantly decreased LRFS for young women with a positive family history, 75.4% versus 98.4% 5-year LRFS for older women. A worse LRFS for young women with a negative lymph node status was also observed, respectively 84% versus 98% 5-year LRFS (both $P<0.001$). In a multivariate analysis, taking into account the pre-treatment and treatment factors, age $\leqslant 40$ years, was the only significant predictor of a decreased LRFS. Thus, young age is an important factor in relation to local control. In a subset analysis, this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and those with a positive family history. To date, there is no evidence that young women with pT1 breast cancer, treated by mastectomy have an improved outcome when compared with those treated with conservative surgery and radiotherapy. Taking into account results from a subset analysis suggests that giving systemic therapy to a subgroup of women who are $\leqslant 40$ years, node-negative and/or have a positive family history might give a better local control.

Keywords: Breast cancer; Breast-conserving therapy; Age; Local control

1. Introduction

Nowadays, breast conservative treatment (BCT) is the standard treatment for small breast tumours, stage I and II. Large randomised trials such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, the European Organization for Research and Treatment of Cancer (EORTC) trial 10801, and other data showed equal results for lumpectomy with irradiation, compared with mastectomy [1–4].

Women with T1 tumours are an excellent group for BCT. In addition, from a psychological and social point of view, BCT offers women a better treatment compared with mastectomy. In this respect, young women are an important group. Many studies report a higher local recurrence rate in young women, ranging from 8 to 31% in women younger than 45 years of age [5–14,29].

The identification of patients at an increased risk of local recurrence after BCT continues to generate controversy. Many factors have been identified. Unfortunately, direct comparison of published data is limited because of differences in surgical and radiation techniques, histological evaluations and the use of adjuvant systemic therapy.

In the EORTC trial, investigating the value of the boost dose, which included 5569 patients, young age (<40 years) was again one of the major prognostic factors for worse local control.

This raises the question of whether BCT is the right primary treatment for young women or whether other factors should be considered. To evaluate the importance of young age as a prognostic factor for local recurrence, we analysed a prospective cohort study of breast cancer patients with T1 tumours, all treated with

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BCT, and all treated with radiotherapy at the Radiotherapy department of the Medisch Spectrum Twente (MST).

2. Patients and methods

Between 1984 and 1997, 1085 patients with a pathological T1 breast cancer (pT1), were treated with BCT in the Twente-Achterhoek region, and all had the radiotherapy at the Radiotherapy Department of the MST.

The standard treatment for BCT consisted of lumpectomy with axillary dissection, clearance level I–III, followed by radiotherapy of the whole breast with a boost to the primary tumour area.

The radiotherapy was 50 Gy to the whole breast delivered by tangential technique in 2 Gy fractions, five times a week. This was followed by a boost to the primary tumour bed of 14 Gy in 2 Gy fractions five times a week, delivered by external photon or electron beam therapy. In the early years, a boost of 15 Gy, 2.5 Gy fractions, four times a week was delivered to 143 patients (13%). 27 patients were treated by an iridium implantation peroperatively with a dose of 15 Gy at a low dose rate.

The adjuvant therapy consisted of regional or parasternal radiotherapy, and of hormonal and/or chemotherapy. 50 Gy was given for regional or parasternal radiotherapy in 2 Gy fractions five times a week. Regional radiotherapy, including axilla, supraclavicular and parasternal, was indicated for patients with more than three positive lymph nodes and/or extranodal disease (EN). Parasternal radiotherapy was indicated for those with less then four positive lymph nodes without EN. Giving parasternal radiotherapy depended also on the medial implantation of the breast, because priority was given to radiotherapy of the breast as part of the primary treatment. This may have led to patients with an indication for parasternal radiotherapy not receiving it.

Until 1992, premenopausal women received chemotherapy when the number of positive lymph nodes was more than three. Nowadays, all premenopausal patients with positive lymph nodes have chemotherapy. Generally, the chemotherapy was administered post-radiotherapy.

For postmenopausal patients, adjuvant hormonal therapy was given when positive lymph nodes were present. All patients underwent a close follow-up every 3 months for the first 3 years and twice a year thereafter. The follow-up included family history, local recurrence, regional recurrence, distant metastasis and survival. For the purpose of this study the cut-off for analysis was July 2000.

As local recurrence and new primaries in the treated breast are often difficult to differentiate, they were all classified as local recurrences. Recurrences in the axilla, parasternal or a combination were classified as regional recurrence. Patients were divided into two groups according to age; either 40 years or younger or older than 40 years of age. The comparability of the two age groups was assessed in terms of clinical factors (localisation of the primary, family history), histopathological factors (histology, presence of carcinoma *in situ* (CIS), involvement margins in the lumpectomy, presence and number of positive lymph nodes, incidence of extranodal disease and oestrogen receptor status) and treatment-related factors (type of radiotherapy and incidence of adjuvant systemic therapy). We defined the presence of CIS by having CIS in the lumpectomy specimen. No distinction was made for an extensive intraductal component. Involvement of the margin's in the lumpectomy specimen was defined as having microscopical involvement of infiltrating carcinoma in the margin.

2.1. Statistical methods

Time to recurrence and follow-up was calculated from the start of the treatment. To test between-group differences for categorical data, Chi-square tests were used, while differences in continuous variables were analysed by the *t*-test, when normal distributions were present. Survival statistics were calculated by the method of Kaplan and Meier. The disease-specific survival, corrected for intercurrent death, was calculated. This means that data on patients who died of other causes were regarded as censored data. The disease-free survival (DFS) is defined by survival without any recurrence. The local recurrence-free survival (LRFS) is defined by survival without local recurrence. For comparing survival distributions we used the logrank test. Multivariate survival analysis was done using Cox regression, while for categorical data, logistic regression was used.

3. Results

Of the 1085 women with a pT1 tumour, only 7.8% (85/1085) were 40 years or younger at the time of the primary treatment. The follow-up ranged from 3 to 194 months with a median of 71 months and a mean of 78 months.

Table 1 shows a comparison in terms of clinical, histological and treatment characteristics between the two age groups. The two groups of women defined by age were homogeneous in terms of family history, pN classification, number of positive lymph nodes, margins in the lumpectomy specimen, and carcinoma *in situ* (CIS). An imbalance was observed for histology ($P<0.001$), oestrogen receptor status ($P<0.001$), and systemic adjuvant therapy ($P=0.002$). Young women had predominantly ductal carcinoma and virtually no tubular

or lobular carcinoma. In addition, young women showed more often a negative receptor, although this result must be treated with caution due to the large number of women with unknown receptor status. Young women also had significantly more adjuvant systemic therapy, although again the numbers in the subgroups were small.

3.1. Local recurrences

The local recurrence rate of all 1085 women was 4.2% (46/1085), and according to age group 10.6% (9/85) in women ⩽40 years, and 3.7% (37/998) in women >40 years of age. The time to local recurrence ranged from 9 to 127 months, with a mean of 45 months. According to the age group, the mean was 43 months for women ⩽40 years and 58 months for older women. The log rank test did not show a significance difference.

In univariate analysis, we analysed the clinical, histopathological and treatment factors for local recurrence-free survival (LRFS) (Table 2). Young women showed a significantly reduced LRFS ($P=0.0046$), respectively

Table 1
Clinical, histopathological and treatment characteristics of 1085 pT1 breast cancer patients according to age

	⩽40 years $n=85$ (%)	>40 years $n=1000$ (%)	P value
Family history			
⩾1 FDR	15 (17.6)	224 (22.4)	
None	68 (80)	761 (76.1)	ns
Unknown	2 (2.4)	15 (1.5)	
Histology			
Ductal carcinoma	79 (92.9)	758 (75.8)	
Lobular carcinoma	1 (1.2)	117 (11.7)	
Tubular carcinoma	0	79 (7.9)	$P<0.001$
Medullar carcinoma	4 (4.7)	17 (1.7)	
Other	1 (1.2)	29 (2.9)	
pN classification			
pN0	60 (70.6)	750 (75)	
pN1	25 (29.4)	236 (23.6)	ns
Unknown		14 (1.4)	
Number of positive lymph nodes			
None	60 (70.6)	749 (74.9)	
1–3	19 (22.4)	189 (18.9)	ns
>3	6 (7.1)	48 (4.8)	
Unknown		14 (1.4)	
Margin in lumpectomy			
Positive	7 (8.2)	85 (8.5)	
Negative	77 (90.6)	906 (90.6)	ns
Unknown	1 (1.2)	5 (0.5)	
Carcinoma *in situ*			
None	58 (68.2)	688 (68.8)	
DCIS	25 (29.4)	254 (25.4)	ns
LCIS	2 (2.4)	58 (5.8)	
Oestrogen receptor			
Positive	19 (55.9)	293 (80.1)	
Negative	15 (44.1)	62 (16.9)	$P<0.001$
Unknown		11 (3)	
Missing $n=685$			
Adjuvant radiotherapy			
None	57 (67.1)	761 (76.1)	ns
Treated	28 (32.9)	239 (23.9)	
Adjuvant systemic therapy			
None	54 (63.5)	780 (78)	$P=0.002$
Treated	31 (36.5)	220 (22)	

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; FDR, first-degree relative; ns, non-significant.

Table 2
Local recurrence related to clinical, histopathological and treatment factors, and differences in local recurrence-free survival (compared by log rank test)

	Local recurrence (2 unknown)		P value
	Present $n=46$ (%)	None $n=1037$ (%)	
Age (years)			
⩽40	9 (10.6)	76 (89.4)	
>40	37 (3.7)	961 (96.7)	$P=0.0046$
Family history			
⩾1 FDR	8 (3.4)	231 (96.6)	
None	37 (4.5)	791 (95.5)	ns
Unknown	1	15	
Histology			
Ductal carcinoma	37 (4.4)	798 (95.7)	
Lobular carcinoma	4 (3.4)	114 (96.6)	
Medullar carcinoma	4 (19)	17 (80)	$P=0.0032$
Tubular carcinoma	1 (1.3)	78 (98.7)	
Rest	0	30	
pN-stage			
pN0	33 (4.1)	777 (956.13)	
pN1	13 (4.6)	246 (95.4)	ns
Unknown	0	14	
Number of positive lymph nodes			
1–3	8 (3.9)	200 (96.1)	
>3	5 (9.3)	48 (90.7)	ns
None	33 (4.1)	776 (95.9)	
Unknown	0	14	
Margin in lumpectomy			
Positive	6 (6.5)	86 (93.5)	
Negative	40 (4)	945 (96)	ns
Unknown	0	6	
Carcinoma *in situ*			
DCIS	15 (5.4)	263 (94.6)	
LCIS	2 (3.4)	58 (96.6)	ns
None	29 (3.9)	716 (96.1)	
Adjuvant radiotherapy			
Treated	16 (6)	250 (94)	ns
None	30 (3.7)	787 (96.3)	
Adjuvant systemic therapy			
Treated	10 (4)	240 (96)	
None	36 (4.3)	797 (95.7)	ns

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; FDR, first degree relative; ns, non-significant.

89% versus 97.4% 5-year LRFS, as well as those with medullar carcinoma ($P = 0.0032$).

In a separate analysis, young women were compared with older women for pretreatment factors in relation to LRFS (Table 3). Young women with a positive family history had a significantly reduced LRFS, 75.4% at 5-years, than women >40 years, 98.4%. This was also the case for young women with a negative lymph node status, 84% versus 98% 5-year LRFS, respectively (both $P < 0.001$). There was also a reduced LRFS for young women without the presence of CIS and for young women with a negative lumpectomy margin, both relative to the older women. The separate analysis for treatment factors showed a reduced LRFS for young women not treated with adjuvant radiotherapy or systemic therapy (Table 4). The separate analysis for the two age categories in relation to adjuvant treatment showed no significant relationship with LRFS (Table 5).

In a multivariate logistic regression for local recurrence, we took into account the pretreatment and treatment factors. A borderline significantly increased risk was seen for women ⩽40 years (OR = 2.3; 95% confidence interval (CI): 1.0–5.3; $P = 0.057$) and significant for medullar carcinoma (OR = 6.1; 95% CI: 1.8–20.6; $P = 0.004$). In the same analysis, adjuvant systemic therapy showed a trend of having a protective effect with respect to local recurrence (OR = 0.3; 95% CI 0.1–1.2; $P = 0.083$).

In a multivariate Cox regression, taking into account the pretreatment and treatment factors from the separate analysis, age ⩽40 years, was the only significant risk factor for a reduced LRFS (OR = 2.4; 95% CI: 1.1–5.3; $P = 0.027$).

The distant metastasis rate was 13.5% for all women; 29.4% (25/85) in women ⩽40 years and 12.2% (122/999) in women >40 years, which was highly significant ($P < 0.001$).

3.2. Survival

The 5- and 10-year disease-specific survival, corrected for intercurrent death, was 84.4 and 66% for women ⩽40 years, respectively, and 93.7 and 87% for older

Table 3
Local recurrence-free survival analysis (log rank test) of the relationship of age and local recurrence according to the pretreatment factors

	Age category	Local recurrence Positive *n* (%)	Negative *n* (%)	*P* value (log rank)	Relative hazard
Family history					
None					
n = 828	⩽40 years	5 (7.4)	63 (92.6)	ns	
	>40 years	32 (4.2)	728 (95.8)		
Positive					
n = 239	⩽40 years	3 (20)	12 (80)	$P < 0.001$	8.1
	>40 years	5 (2.2)	219 (97.8)		0.9
Lymph node status					
Negative					
n = 810	⩽40 years	8 (13.3)	52 (86.7)	$P < 0.001$	3.8
	>40 years	25 (3.3)	725 (96.7)		0.9
Positive					
n = 259	⩽40 years	1 (4)	24 (96)	ns	
	>40 years	11 (4.7)	223 (95.3)		
Margin in lumpectomy					
Negative					
n = 985	⩽40 years	8 (10.4)	69 (89.6)	$P = 0.008$	2.5
	>40 years	32 (3.5)	876 (96.5)		0.9
Positive					
n = 92	<40 years	1 (14.3)	6 (85.7)	ns	
	>40 years	5 (5.9)	80 (94.1)		
In situ carcinoma					
None					
n = 745	⩽40 years	6 (10)	52 (86.7)	$P = 0.02$	2.5
	>40 years	23 (3.3)	664 (96.7)		0.9
DCIS					
n = 278	⩽40 years	3 (12)	22 (88)	ns	
	>40 years	12 (4.7)	241 (95.3)		
LCIS					
n = 60	⩽40 years	0	2	ns	
	>40 years	2 (3.4)	56 (96.6)		

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; ns, non-significant.

Table 4
Local recurrence-free survival analysis of the relationship of age and local recurrence according to the treatment factors

	Age category	Local recurrence (2 unknown)		*P* value (log rank)	Relative hazard
		Positive *n* (%)	Negative *n* (%)		
Adjuvant radiotherapy					
None					
$n=817$	⩽40 years	6 (10.5)	51 (89.5)	$P=0.0036$	3.2
	>40 years	24 (3.2)	736 (96.8)		0.9
Treated					
$n=266$	⩽40 years	3 (10.7)	25 (89.3)	ns	
	>40 years	13 (5.5)	225 (94.5)		
Adjuvant systemic therapy					
None					
$n=833$	⩽40 years	8 (14.8)	46 (85.2)	$P<0.001$	3.7
	>40 years	28 (3.6)	751 (96.4)		0.9
Treated					
$n=250$	⩽40 years	1 (3.2)	30 (96.8)	ns	
	>40 years	9 (4.1)	210 (95.9)		

ns, non-significant.

women (log rank test, $P<0.001$). The 5-year disease-free survival (survival without any recurrence) was 71.2% for women ⩽40 years and 88.8% for the older women ($P<0.001$) (Fig. 1). The local recurrence-free survival (survival without local recurrence) was significantly different for the two age groups, 89%, for women ⩽40 years, and 97.6% for those >40 years ($P=0.0046$) (Fig. 2). In a separate analysis, young women were compared with older women for family history, lymph node status, margin in the lumpectomy specimen, *in situ* carcinoma, adjuvant radiotherapy and adjuvant systemic therapy pretreatment and treatment factors in relation to disease-specific survival (Table 6).

In a multivariate Cox regression analysis, taking into account age, family history, histology, lymph node status, CIS, contra-lateral breast cancer, adjuvant radiotherapy and adjuvant systemic therapy, a significantly higher risk for a reduced disease-specific survival was seen for young women, ⩽40 years of age, (Hazard Ratio (HR) = 2.0; 95% CI: 1.2–3.4; $P=0.007$) and a significantly lower risk was observed for lobular carcinoma compared with ductal carcinoma (HR = 0.1; 95% CI: 0.0–0.9; $P=0.04$).

4. Discussion

In our analysis, young age was demonstrated to be an important prognostic factor in a failure of local control. In addition, age was a major prognostic factor for survival.

Table 5
Local recurrence-free survival analysis of the relationship of treatment factors and local recurrence according to age category

Age category	Adjuvant therapy	Local recurrence (2 unknown)		*P* value (log rank)	Relative hazard
		Positive *n* (%)	Negative *n* (%)		
⩽40 years	Radiotherapy			ns	
$n=85$	Treated	3 (10.7)	25 (89.3)		
	None	6 (10.5)	51 (89.5)		
	Systemic therapy				
	Treated	1 (3.2)	30 (96.8)	$P=0.072$	0.4
	None	8 (14.8)	46 (85.2)		1.8
>40 years	Radiotherapy			ns	
$n=998$	Treated	13 (5.5)	225 (94.5)		
	None	24 (3.2)	736 (96.8)		
	Systemic therapy			ns	
	Treated	9 (4.1)	210 (95.9)		
	None	28 (3.6)	751 (96.4)		

ns, non-significant.

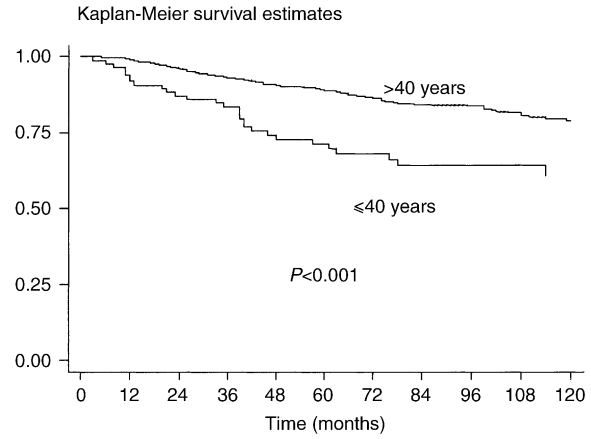

Fig. 1. The disease-free survival rate of 1085 pT1 breast cancer patients according to age.

The clinical factors, such as the localisation of the primary in the breast and the family history with respect to first-degree relatives, showed no differences with respect to local recurrence rate, which is in accordance with the literature [6,14–16,27]. In contrast to the overall analysis, a separate analysis showed that women with a positive family history and aged $\leqslant 40$ years had a significant higher local recurrence rate. This might indicate that the suggested negative effect of a positive family history is limited to young women [27]. Fourquet and Touboul showed that local control was also impaired by premenopausal status [13,17].

Histopathological prognostic factors for local recurrence in breast cancer following BCT vary in the literature. Medullar carcinoma was a prognostic factor for local failure in our analysis. Nevertheless, this result should be viewed with caution because of the small number of patients with a medullar carcinoma and further analysis with a larger cohort of medullar carcinoma should be done to confirm this data.

The multivariate survival analysis showed a 10 times better survival of those patients with lobular carcinoma.

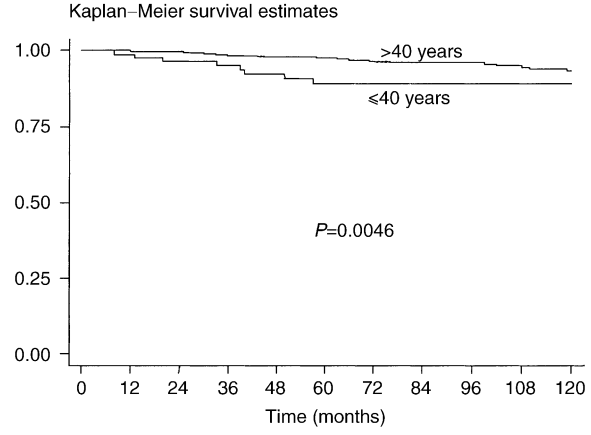

Fig. 2. The local recurrence-free survival of 1083 pT1 breast cancer patients according to age.

Because of the small number with a known grade of differentiation, only 21%, we did use this information in our analysis. This means we cannot compare our results with those of Kollias, who explained the worse prognosis they observed for young patients as being due to the higher proportion of poorly differentiated tumours in this age group [28].

Table 6
Disease-specific survival analysis for the relationship of age according to the pretreatment and treatment factors

	Age category	*P* value (log rank)	Relative hazard
Family history			
None			
$n=829$	$\leqslant 40$ years	$P=0.0085$	2.1
	>40 years		0.9
Positive			
$n=239$	$\leqslant 40$ years	$P=0.03$	3.7
	>40 years		0.9
Lymph node status			
Negative			
$n=810$	$\leqslant 40$ years	$P<0.001$	3.5
	>40 years		0.9
Positive			
$n=261$	$\leqslant 40$ years	ns	
	>40 years		
Margin in lumpectomy			
Negative			
$n=987$	$\leqslant 40$ years	$P<0.001$	2.4
	>40 years		0.9
Positive			
$n=92$	$\leqslant 40$ years	ns	
	>40 years		
In situ carcinoma			
None			
$n=745$	$\leqslant 40$ years	$P=0.0034$	2.2
	>40 years		0.9
DCIS			
$n=278$	$\leqslant 40$ years	$P=0.0054$	2.6
	>40 years		0.9
LCIS			
$n=60$	$\leqslant 40$ years	ns	
	>40 years		
Adjuvant radiotherapy			
None			
$n=818$	$\leqslant 40$ years	$P<0.001$	3.5
	>40 years		0.9
Treated			
$n=267$	$\leqslant 40$ years	ns	
	>40 years		
Adjuvant systemic therapy			
None			
$n=833$	$\leqslant 40$ years	$P=0.0003$	3.1
	>40 years		0.9
Treated			
$n=250$	$\leqslant 40$ years	ns	
	>40 years		

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; ns, non-significant.

Despite the small number of women with a known oestrogen receptor status (400/1085), we found significantly more oestrogen-negative receptors in young women ($P<0.001$), a finding also noted by Kurtz and colleagues [6]. However, de la Rochefordiere and colleagues [22] noted no significant difference in the oestrogen receptor status for young women. However, because of the small number of patients with a known oestrogen receptor status, this factor was excluded in the multivariate analysis.

Recht and colleagues [5] showed the presence of an extensive intraductal component (EIC) to be an important prognostic factor. Young women had a higher incidence of EIC, but even in the absence of EIC the local recurrence rate was still higher for young women. In addition, Boyages and colleagues, Veronesi and colleagues, and others showed EIC to be an important factor [9,13,17–19]. In the present study, we noted that the presence of CIS in the lumpectomy specimen was not related to a significantly higher incidence rate of local recurrence. In our separate analysis, young women had a significantly reduced LRFS in the absence of DCIS or LCIS. Both with and without CIS, a high rate of local recurrence was found in young women. Probably because of the low numbers, this did not reach statistical significance. The data from the literature suggest the presence of an EIC may be related to a higher local recurrence rate.

Inadequate or positive margins are seen in many studies as an important risk factor for local recurrence [10,13,19,20,25]. Solin and colleagues, unlike many other reports did not note a higher incidence rate but in agreement with our results, associated with positive margins [23]. In the separate analysis, for young versus older women, both positive and negative margins were associated with a higher rate of local recurrence in young women, although this was not statistically significant for the positive margins, possibly because of the small number of patients. The differing reports in the literature could be explained by the difficulties encountered in comparing these kinds of data due to the lack of uniformly accepted definitions of positive and negative margins. We defined positive margins as having infiltrating carcinoma present at an inked surface of the specimen. Close to the surface was considered as negative. In contrast with other data, the presence of CIS was not taken into account with respect to the margin status [25].

The presence of positive lymph nodes was an independent predictor for local recurrence in a study by Dalberg and colleagues, a result we did not confirm [21]. In our study, we noted that the adverse effect of young age was limited to the node-negative patients, which is in accordance with other data [12,26]. The same was seen in the separate disease-specific survival analysis.

In the univariate analysis, adjuvant treatment whether with radiotherapy or with systemic therapy, did not show a relationship to local recurrence. In the separate analysis, the reduced LRFS for young women was limited to the patients not treated with adjuvant therapy. Whether adjuvant treatment might reduce the LRFS in young women was examined in a separate analysis (Table 5). Only a trend was seen in the group of patients treated with adjuvant systemic therapy in contrast to the group of adjuvant radiotherapy, in which both treated and untreated young women, had a high LRFS. From the adjuvant systemic therapy data, it looks as if giving young node-negative patients adjuvant systemic therapy might reduce the local recurrence rate. However, due to the small number of young women in the subgroups, we have to interpret this data with caution.

In a multivariate logistic regression analysis for local recurrence in relation to pre-treatment and treatment factors, young age was a borderline significant risk factor with an OR of 2.3 (95% CI: 1.0–5.3). In the same analysis, adjuvant systemic therapy showed a clear trend of having a protective effect with respect to local recurrence, which supports the conclusion by Elkhuizen [26]. However, the Cox regression analysis for disease-specific survival and local recurrence-free survival could not confirm the benefit of adjuvant systemic therapy, but showed young age to be a clear significant risk factor. This data is in accordance with results by Fourquet and Locker, who also found young age to be an independent significant factor [13,29].

The high local recurrence rate in young women was accompanied by an even higher rate of distant metastases; 29.4% for young women compared with 12.2% for older women ($P<0.001$). This increased incidence has been noted in several other studies [8,11,12,14, 18,22], which supports the idea of giving adjuvant systemic therapy to young women.

Finally, the high recurrence rate in young women was clearly shown in the reduced disease-specific survival. To conclude, young women with pT1 breast cancer, undergoing conservative surgery and radiotherapy, fare significantly worse compared with older women, in terms of local control, distant metastases and survival. In a subset analysis, this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and patients with a positive FH. To date, there is no evidence that young women with pT1 breast cancer, treated by mastectomy have an improved outcome when compared with those treated with conservative surgery and radiotherapy.

Young age is generally accepted as a prognostic factor. Nevertheless, it is not regarded as a factor in determining certain adjuvant treatment. Whether young age should be regarded as a treatment-related prognostic factor is doubtful. Future and ongoing treatment with more adjuvant systemic therapy might provide answers.

Prospective randomised studies for this category of women are therefore necessary, and might provide new prognostic and predictive factors, as stated by Hayes [24]. However, young women, $\leqslant 40$ years of age, with breast cancer are a small group. In this respect, prospective cohort studies might be important in answering these questions.

References

1. Fischer B, Bauer M, Margolese R, *et al*. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Eng J Med* 1985, **312**, 665–673.
2. Van Dongen JA, Fentiman IS, Lerut T, *et al*. Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer, EORTC 10801. *J Natl Cancer Inst Mon* 1992, **11**, 15–18.
3. Arriagado R, Lê MG, Rochard F, *et al*. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. *J Clin Oncol* 1996, **14**, 1558–1564.
4. Veronesi U, Banfi A, Salvadori B, *et al*. Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomised trial. *Eur J Cancer* 1990, **26A**, 668–670.
5. Recht A, Connolly JL, Schnitt SJ, *et al*. The effect of young age on tumor recurrence in the treated breast after conservative surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 1988, **14**, 3–10.
6. Kurtz JM, Spitalier JM, Amalric R, *et al*. Mammary recurrences in women younger than forty. *Int J Radiat Oncol Biol Phys* 1988, **15**, 271–276.
7. Neff PT, Bear HD, Pierce CV, *et al*. Long-term results of breast conservation therapy for breast cancer. *Ann Surg* 1996, **223**, 709–716.
8. Braud AC, Asselain B, Scholl S, *et al*. Neoadjuvant chemotherapy in young breast cancer patients: correlation between response and relapse? *Eur J Cancer* 1999, **35**, 392–397.
9. Boyages J, Recht A, Connolly JL, *et al*. Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radioth Oncol* 1990, **19**, 29–41.
10. Borger J, Kemperman H, Hart A, *et al*. Risk factors in breast-conservation therapy. *J Clin Oncol* 1994, **12**, 653–660.
11. Elkhuizen PH, van de Vijver MJ, Zonderland HM, *et al*. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Radiat Oncol Biol Phys* 1998, **40**, 859–867.
12. Fowble BL, Schultz DJ, Overmoyer B, *et al*. The influence of young age on outcome in early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1994, **30**, 23–33.
13. Fourquet A, Campana F, Zafrani B, *et al*. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989, **17**, 719–725.
14. Haas JA, Schultz DJ, Peterson ME, *et al*. An analysis of age and family history on outcome after breast-conservation treatment: the University of Pennsylvania experience. *Cancer J Sci Am* 1998, **4**, 308–315.
15. Chabner E, Nixon A, Gelman R, *et al*. Family history and treatment outcome in young women after breast-conserving surgery and radiation therapy for early-stage breast cancer. *J Clin Oncol* 1998, **16**, 2045–2051.
16. Harrold EV, Turner BC, Matloff ET, *et al*. Local recurrence in the conservatively treated breast cancer patient: a correlation with age and family history. *Cancer J Sci Am* 1998, **4**, 302–307.
17. Touboul E, Buffat L, Belkacemi Y, *et al*. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys* 1999, **43**, 25–38.
18. Veronesi U, Marubini E, Del Vecchio M, *et al*. Local recurrence and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995, **87**, 19–27.
19. Burke MF, Allison R, Tripcony L. Conservative therapy of breast cancer in Queensland. *Int J Radiat Oncol Biol Phys* 1994, **31**, 295–303.
20. Dewar JA, Arriagada R, Benhamou S, *et al*. Local relapse and contralateral tumor rates in patients with breast cancer treated with conservative surgery and radiotherapy (Institut Gustave Roussy 1970-1982). IGR Breast Cancer Group. *Cancer* 1995, **76**, 2260–2265.
21. Dalberg K, Mattsson A, Rutqvist LE, *et al*. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast recurrences. *Breast Cancer Res Treat* 1997, **43**, 73–86.
22. de la Rochefordiere A, Asselain B, Campana F, *et al*. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993, **341**, 1039–1043.
23. Solin LJ, Fowble BL, Schulz DJ, *et al*. The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1991, **21**, 279–287.
24. Thomssen C, Kaufmann M, Hayes DF, *et al*. Do we need better prognostic factors in node-negative breast cancer? *Eur J Cancer* 2000, **36**, 293–306.
25. Wazer DE, Schmidt-Ullrich RK, Ruthazer R, *et al*. The influence of age and extensive intraductal component histology upon breast lumpectomy margin assessment as a predictor of residual tumor. *Int J Radiat Oncol Biol Phys* 1999, **45**, 885–891.
26. Elkhuizen PHM, Slooten van H-J, Clahsen PC, *et al*. High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of perioperative chemotherapy: a European Organization for Research and Treatment of Breast Cancer Cooperative Group Study. *J Clin Oncol* 2000, **18**, 1075–1083.
27. Jobsen JJ, Palen van der J, Meerwaldt JH. Family history in breast cancer is not a prognostic factor? *Breast* 2000, **9**, 83–87.
28. Kollias J, Elston CW, Robertson JFR, *et al*. Early-onset breast cancer — histopathological and prognostic considerations. *Br J Cancer* 1997, **75**, 1318–1323.
29. Locker AP, Ellis IO, Morgant DAL, *et al*. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg* 1989, **76**, 890–894.