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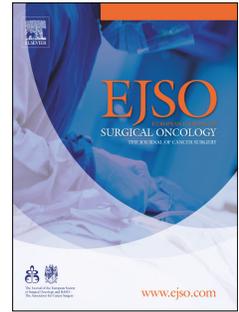
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**The impact of margin status in breast-conserving therapy for lobular carcinoma
is age related**

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Key words. Breast conserving therapy, lobular carcinoma, margin status, age, outcome

Abstract.

Purpose. The aim is to look at the impact of margin status and outcome of invasive lobular carcinoma (ILC) treated with breast-conserving therapy (BCT).

Methods. This manuscript describes an analysis on 330 BCT in 318 patients with ILC.

Results. The 12-year local relapse free survival (LRFS) is 89%. In multivariate analysis, positive margin status, age >50-years, contra lateral breast cancer, and adjuvant systemic therapy were significant predictors of local relapse free survival.

In a separate analysis limited to a positive margin for invasive carcinoma or carcinoma in situ, only a positive margin for invasive carcinoma was a significant predictor of local relapse free survival. This was limited to women \leq 50 years.

The 12-year disease-specific survival (DSS) was 85%. In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 7.2), and a tumour size of pT2 (HR 2.5) were significant independent predictors of disease-specific survival (DFS). These factors were also relevant for distant metastasis-free survival (DMFS) and disease-free survival (DFS).

Conclusions. Positive margins for invasive carcinoma seem to be a strong predictor for local recurrence in particular for women \leq 50-years. Our study showed grade 3 and tumour size to be strong predictors of DMFS, DFS, and DSS. Margin status was not.

Introduction.

Over the last two decades, the trend in breast cancer management has been towards less invasive treatment strategies. Several large-scale studies have demonstrated that breast-conserving therapy (BCT) consisting of lumpectomy and radiation treatment is as effective as mastectomy.^{1,2} These studies validating the use of BCT were not designed to look at histology as an independent variable affecting the outcome. The overall outcome has been heavily weighted by the most common histological type, invasive ductal carcinoma. Invasive lobular carcinoma (ILC) is the second most common type, accounting for 8-16% of all invasive breast cancers.^{3,4} Because of differences in histological features for ILC, such as a more infiltrative growth pattern, a more frequent discontinuity, and a less defined thickening, and the differences in clinical behaviour, there has been a preference toward treating patients with more aggressive surgery instead of BCT.⁵ And, hence, not entering these patients in BCT trials.

Because studies show that the incidence of ILC has increased over the last 10-20 years, particularly in post-menopausal women, ILC has been the subject of increasing interest.⁴⁻⁶

Irrespective of histology, many studies have focused on identifying factors that may affect local control after BCT such as margin status, presence of in situ carcinoma, tumour size, and grade. In earlier studies we established a difference in outcome for the different involvements of the margin by invasive carcinoma or carcinoma in situ, but these studies were heavily weighted by invasive ductal carcinoma too.^{7,8} In a large study by Sastre et al. no difference was shown in local control between ILC and non-ILC.⁹ In a large sized study derived from the National Cancer Data Base, Winchester et al. found no difference in overall survival between ILC and non-ILC cases comparing BCT to mastectomy.¹⁰

The purpose of the current study is to look at the long-term outcome and the impact of margin status of ILC treated with BCT from a single region in the Netherlands during the last twenty years.

Patients and Methods.

This prospective cohort of breast cancer patients was started in 1983 when BCT was introduced in our region. All patients in the Twente-Achterhoek region with invasive breast cancer, treated with BCT received their irradiation at the Radiotherapy Department of the Medisch Spectrum Twente at Enschede. All patient data, including demographics, histology, staging information, treatment, and outcome were recorded prospectively

and updated regularly by the first author. From 1983 through 2005 a total of 2923 BCT were registered in 2836 patients. The histology from these 2923 BCT consisted of 2227 (76%) invasive ductal carcinoma, 330 (11%) invasive lobular carcinoma (ILC), 124 (4%) invasive tubular carcinoma, 51 (2%) medullary carcinoma, and the rest mucinous carcinoma, undifferentiated carcinoma, or a combination of invasive ductal, lobular, or tubular carcinoma. This manuscript describes an analysis on the 330 BCT in 318 patients with ILC. None of the patients was lost to follow-up.

Histological examination for all BCT was done in the Pathology of Laboratory Oost Nederland. When missing the histological criteria of the ILC were up dated before analysis and reviewed by one pathologist. Patients were classified according to the TNM-classification, 4th edition 1997.

We defined synchronous bilateral breast cancer (BBC) as cancer diagnosed in both breasts simultaneously or within a period of 3 months of diagnosis of the first tumour. Metachronous contra lateral breast cancer (CBC) was defined as breast cancer occurring in the contra lateral breast more than 3 months after the diagnosis of the tumour in the first breast affected.

As it is often difficult to differentiate between a local recurrence and a new primary in the treated breast, all tumours found in the ipsi-lateral breast during follow-up were classified as local recurrences.

All patients were seen every 3 months for the first 2 years and twice a year thereafter. During follow-up local recurrence, regional recurrence, distant metastasis, and survival were noted. For the purposes of this study, the cut-off for analysis was September 2008.

Margin status.

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma (IC) or carcinoma in-situ (CIS) at the inked margin. Close margins were recorded as negative. Massive involvement with IC or CIS of the margins, defined as diffuse or multiple microscopic foci, was regarded as an indication for a re-excision. In case of focal microscopic involvement of the margin the surgeon was advised not to re-excise. The policy in our department was that minimal microscopic disease should be treated with radiotherapy. After our first study in 2003 this was changed, the aim was to have clear margins.⁸ In total 33 re-excisions were performed. Negative margins were defined as having no microscopic involvement of the inked margin with IC and/or CIS of the lumpectomy specimen or after re-excision.

Of all 318 patients accounting for 330 BCT the status of the resection margins was known.

Treatment.

BCT consisted of lumpectomy with axillary clearance of levels I-III or sentinel node procedure, the latter being introduced in 2001, followed by radiotherapy to the whole breast with a boost to the primary tumour area. The radiotherapy regimen consisted of 50 Gy to the whole breast, followed by a 14 Gy boost to the primary tumour bed. The boost dose given was similar for all patients, regardless of margin status. The localization of the boost was determined by the location of the scar, the primary tumour location, the mammography, and if possible by radiopaque clips placed during the lumpectomy procedure.

Adjuvant therapy consisted of radiotherapy to the regional lymph nodes or to the internal mammary chain only and hormonal and/or chemotherapy. Regional radiotherapy, which included the axilla and the supraclavicular, and internal mammary chains, was indicated for patients with four or more positive lymph nodes and/or extra nodal disease (EN). Radiotherapy of the internal mammary chain only was indicated for those patients with less than four positive lymph nodes and no EN. In case of medial implantation of the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

In the late eighties adjuvant systemic therapy was introduced for patients with positive nodes. From 1992 on, all premenopausal patients with positive lymph nodes received chemotherapy. For postmenopausal patients adjuvant hormonal therapy was given when positive lymph nodes were present. Since 1999 indications for adjuvant systemic therapy depended not only on the lymph node status, but also in case of a negative lymph node status on the mitotic activity index, histological grade and tumour size. Premenopausal women received chemotherapy and endocrine therapy when the estrogens receptor status was positive. Postmenopausal women received primarily endocrine therapy and were offered chemotherapy if younger than < 70 years. With a hormone receptor negative status patients were offered chemotherapy.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of BCT. To test between-group differences for categorical data Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to *the number of BCT*. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the time of analysis or if they were lost to follow-up or were dead, without disease, at the time of analysis. The local recurrence-free survival (LRFS) is

defined as survival without local recurrence. An event was defined as the occurrence of a local recurrence in the treated breast.

Statistics for distant metastasis and survival were performed in relation to *the number of patients* and calculated by the method of Kaplan and Meier. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated in relation to the number of patients. This means that for this particular analysis, data on patients who died of other causes than breast cancer were regarded as censored data. An event was defined as death due to breast cancer. The distant metastasis-free survival (DMFS) is defined as survival without distant metastasis in patients. An event was defined as the occurrence of distant metastasis in the patient.

For comparison of survival distributions the log-rank test was used. Variables that were univariately related to the outcomes of interest ($p < 0.05$) were entered in the multivariate analyses.

The Cox proportional hazards model was used to test for the independent effect of margins status after adjusting for known prognostic factors and hazard ratios (HR) estimated with 95% confidence limits are presented. With an overall median follow-up of 95 months all analysis were performed on 12-year follow-up.

In the univariate analysis we used the following variables: age, localisation of the primary in the breast, family history, re-excision status, margin status, grade of differentiation, presence of lymph vascular space involvement, oestrogen status, progesterone status, mitotic activity index, tumour size, lymph node status, BBC, CBC, adjuvant radiotherapy, and adjuvant systemic therapy.

All analyses were performed using STATA.¹¹

Results.

Of the 318 patients with ILC and treated with 330 BCT the age ranged from 34-83 years with a mean and median age of 60-years. Only 7 patients (2%) were aged ≤ 40 -years.

The clinical, patho-histological, and treatment characteristics of all 330 BCT are presented in table 1 and 2.

Three patients (1%) presented with BBC, and 33 patients (10%) developed CBC. The median time to CBC was 57 months.

Local control

Of the 330 BCT 6% (21/330) developed a local recurrence during follow-up. The 5-, 10-, and 12-year local relapse free survival (LRFS) is 97%, 92.2%, and 89% respectively. The time to local recurrence ranged from 18-199 months with a median of 83 months.

The univariate analysis showed age, CBC, positive margins for invasive carcinoma (IC) and/or lobular carcinoma in situ (LCIS), and adjuvant systemic therapy to be significant predictors for local recurrence.

In the multivariate analysis with the above mentioned factors, positive margin status (HR 3.5; 95% CI 1.37-9.03; $p=0.009$), age >50-years (HR 0.25; 95% CI 0.09-0.63; $p=0.003$), CBC (HR 4.9; 95% CI 1.77-13.63; $p=0.002$), and adjuvant systemic therapy (HR 0.13; 95% CI 0.02-0.99; $p=0.049$) were independent significant predictors for local recurrence.

In a separate analysis on positive margin status for IC, LCIS and IC plus LCIS, only positive margin for IC (HR 3.5) and positive for IC plus LCIS (HR 4.9) showed significance (table 3). This increased risk is most pronounced in women ≤ 50 years (fig 1). Due to the small numbers for LCIS and also for the women ≤ 50 years the confidence intervals are large and results should be interpreted with caution.

Distant metastasis

The incidence rate for distant metastasis of the 318 patients was 13% (42/318). The 5-, 10-, and 12-years distant metastasis-free survival (DMFS) was 91%, 84.5%, and 83%, respectively. Time to metastasis ranged from 9-215 months with a median of 58 months.

The univariate analysis showed significance for the following characteristics: differentiation grade, tumour size, lymph node status, adjuvant radiotherapy and systemic therapy.

In multivariate Cox regression analysis including the above mentioned factors grade 3 compared to grade 2 (HR 6.9; 95% CI 3.2-15.0; $p<0.001$) was a significant predictor of distant metastasis, as well as a tumour size of pT2 (HR 3.2; 95% CI 1.7-6.3; $p<0.001$), and a tumour positive lymph node status (HR 7.7; 95% CI 2.2-27.2; $p=0.001$).

Disease-free survival

The 5-, 10-, and 12-year disease-free survival (DFS) for the 318 patients was 90%, 80 and 77%, respectively.

Univariate analysis showed differentiation grade, tumour size, and margin status for IC and/or LCIS to be significantly related to DFS.

In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 3.3; 95% CI 1.7-6.5; $p<0.001$), and large tumour size (pT2) (HR 2.4; 95% CI 1.3-4.4; $p=0.004$) were independent predictors of DFS.

Disease-specific survival

The 5-, 10-, and 12-year disease-specific survival (DSS) for the 318 patients was 97%, 93%, and 85%, respectively.

The univariate analysis showed differentiation grade (fig.2), tumour size, lymph node status, adjuvant radiotherapy, and systemic therapy to be significantly related to DSS.

In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 7.2; 95% CI 2.8 – 18.9; $p < 0.001$), and a tumour size of pT2 (HR 2.5; 95% CI 1.1-5.9; $p = 0.034$) was an independent predictor of DSS. Tumour positive lymph nodes (HR 4.4; 95% CI 0.9-20.2; $p = 0.060$) showed borderline significance.

Discussion.

This study shows positive margins for IC to be a predictive factor for local recurrence in women with invasive lobular carcinoma, but this seem limited to women ≤ 50 -years. With respect to distant metastasis and survival the usual suspect such as grading, tumour size, and lymph node status are important prognostic factors, but margin status was not.

This prospective cohort of all breast cancer patients treated with BCT was started in 1987 by the first author. The data are updated regularly on recurrence status, family history and status of the patient. All patients are followed even when they move to other parts of the country, keeping the loss to follow-up to an absolute minimum. Data are checked before entering the dataset by the first author personally.

Local control and margin status

The local recurrence rate of 8% at 10-years for ILC in our study is comparable to the overall 10-year local recurrence rate of for instance EORTC 22881-10882 trial and our own results.^{7, 8, 12}

Despite the acceptance of BCT to be the primary treatment in early staged breast cancer, there is still debate over what is the appropriate margin. It is generally accepted that involved margins are associated with a higher local recurrence rate, only there is no consensus on the definition of clear surgical margins. As mentioned earlier, positive margins in this study were those with invasive carcinoma or carcinoma in situ in the inked margin.^{13, 14} ILC may infiltrate the breast stroma and adipose tissue insidiously without producing a discrete mass. So, it is conceivable that in some patients with ILC after lumpectomy a considerable tumour burden still remained in the vicinity of the lumpectomy cavity. This might not only explain the high percentage of positive resection margins 18- 63% in the literature, but also the reported high local recurrence rates.¹⁵⁻¹⁹ In this respect a positive margin

status might be an important risk factor for developing local recurrence after BCT.²⁰ However this was not confirmed by a recent study in 416 patients with ILC by van den Broek et al.²¹

In our study 30% (100/330) of the cases showed positive margins after first excision. After 33 re-excisions 22% (72/330) cases with positive margins for IC, CIS or both remained. This is a rather high percentage but can be explained by our policy in the early years not to re-excise cases with only focal positive margins.^{7,8} The high rate of positive margins did however not translate into a high local recurrence rate. Looking at the relation between positive margin status and local control, we found significance for positive margin for IC and for both, LCIS and IC. LCIS alone did not show significance in relation to local control. Further analysis showed a relation between age and margin status with respect to local control. In an earlier study we showed a statistical interaction between age and margin status, but these studies were heavily weighted by the most common histological type, invasive ductal carcinoma.^{7,8} This study also showed that a positive margin status for IC resulted in high local recurrence rate for women ≤ 40 -years. In the present study we could not show statistical interaction between margin status and age, but still found a strong correlation between age and margin status for IC. Women ≤ 50 -years with positive margins for IC had a seven times higher risk of local recurrence compared to women with negative margins. In general the age of 40 is accepted as an important turning point for patients with breast cancer, and those who are younger show a significantly worse outcome compared to the older category. However, most studies are heavily weighted by invasive ductal carcinoma. Our study with only 7 women ≤ 40 -years and a median age of 60-years shows that ILC seems to be seen mostly in an older age category compared to invasive ductal carcinoma. In our series of only ILC we found a possible turning point at 50-years, but only for local control, suggesting positive margin status for ILC to be particularly important for women ≤ 50 -years. Age was not an important factor for either distant metastasis or survival for patients with ILC.

The presence of lobular carcinoma-in-situ (LCIS) at the lumpectomy margin is in general regarded as irrelevant. Some investigators have noted that ILC and ILC coexisting with LCIS have an increased risk of in-breast events, but in both scenarios the excess breast events tend to occur over a protracted follow-up. This suggests an increased long-term risk of developing new primary breast lesions.^{22,23} Our study shows a trend towards an increased local recurrence rate with positive margins for LCIS, only this seems limited to women > 50 -years.

Metastasis and survival

As expected, histological grading, tumour size, and lymph node status were the most important predictive factors for DMFS, DFS, and DSS.

A study by Møller Talman et al. including 860 ILC showed a significant worse prognosis for grade 3 tumours compared to grade 2 regarding both DFS and overall survival.⁶ The Nottingham group showed that histological grading was the most important factor in predicting prognosis.²² Our material included 330 ILC with 17% grade 1, 72% grade 2, and 10% grade 3 tumours. We also found a worse prognosis for grade 3 compared to grade 2 for DMFS, DFS and DSS. Singletary et al in a large series showed tumour size and lymph node status to be the most important predictive factors for DFS.⁵ A recent paper of Rakha et al showed lymph node status to be the strongest predictor of both DSS and DFS for patients with ILC followed by grade, vascular invasion, size, and ER status.¹⁸ Our study showed tumour size and in particularly lymph node status to be strong predictors of DMFS, DFS, and DSS.

Invasive lobular carcinoma has been associated with a higher risk of contra lateral tumours compared to ductal carcinoma. In accordance with the literature we found 1% BBC and 10% CBC rate.^{3, 8, 19, 20}

Conclusions.

Positive margins for IC seems to be a predictive factor for local recurrence in women with invasive lobular carcinoma, but this seem limited to women ≤ 50 -years. Our study showed differentiation grade and tumour size to be strong predictors of DMFS, DFS, and DSS.

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Table 1. Clinical and pathological characteristics of 330 invasive lobular carcinomas all treated with breast-conserving therapy. The patient-related characteristics are based on 318 patients, while carcinoma-related characteristics are based on 330 carcinomas.

Characteristics	N=330 (%)
Age	
≤50 years	69 (21.7)
51-60 years	93 (29.2)
>60 years	156 (49.1)
Family history	
positive	74 (23.3)
negative	244 (76.7)
Localisation primary	
lateral	207 (62.7)
medial/central	123 (37.3)
Differentiation grade	
grade 1	75 (22.7)
grade 2	218 (66.1)
grade 3	32 (9.7)
unknown	5 (1.5)
Lymph vascular space invasion	
positive	9 (2.7)
negative	318 (96.4)
unknown	3 (0.9)
Oestrogen receptor	
positive	306 (92.7)
negative	20 (6.1)
unknown	4 (1.2)
Progesterone receptor	
positive	253 (76.7)
negative	71 (21.5)
unknown	6 (1.8)
Presence of CIS	
DCIS	15 (4.5)
LCIS	118 (35.8)
none	197 (59.7)
Mitotic Activity Index	
low: <13	285 (86.4)
high: >12	37 (11.2)
unknown	8 (2.4)
Re-excision	
yes	33 (10)
none	294 (89.1)
unknown	3 (0.9)
Margin Status	
negative	258 (78.2)
positive IC	38 (11.5)
positive LCIS	25 (7.6)
positive IC+LCIS	9 (2.7)
Tumour size	
≤ 10 mm	89 (27)
11-20 mm	157 (47.6)
21-50 mm	73 (22.1)
pT1mult	11 (3.3)
Lymph node status	
negative	247 (74.8)
1-3 positive nodes	62 (18.8)
> 3 positive nodes	21 (6.4)

IC: invasive carcinoma; LCIS: lobular carcinoma in situ

Table 2. Adjuvant treatment characteristics of 330 breast-conserving treatments of invasive lobular carcinoma of the breast.

Characteristics	number (%)
Adjuvant regional Radiotherapy	
yes	58 (17.6)
none	272 (82.4)
Adjuvant Systemic Therapy	
chemotherapy	10 (3.0)
Hormonal therapy	75 (22.7)
chemo + hormonal therapy	24 (7.3)
none	221 (67.0)

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Table 3. Hazard ratios, confidence interval and p-value for local recurrence at 12-years according to margin status and age category.

Margin status	Hazard Ratio	95% Confidence Interval	p-value
All ages (n=330)			
Negative (n=258)	1		
Positive IC (n=38)	3.5	1.20 – 10.3	0.022
Positive IC + LCIS (n=9)	4.9	1.08 – 22.5	0.040
Positive LCIS (n=25)	2.6	0.57 – 12.1	0.214
Age ≤ 50-years (n=69)			
Negative (n=54)	1		
Positive IC (n=7)	7.3	1.83 – 29.5	0.005
Positive IC + LCIS (n=3)	7.1	1.30 – 39.5	0.024
Positive LCIS (n=5)	-*	-	-
Age > 50-years (n=261)			
Negative (n=204)	1		
Positive IC (n=31)	1.2	0.14 – 9.7	0.888
Positive IC + LCIS (n=6)	-*	-	-
Positive LCIS (n=20)	4.5	0.89 – 22.7	0.067

IC: invasive carcinoma; LCIS: lobular carcinoma in situ

*Cannot be calculated because no local recurrences were observed.

Fig.1 The 12-year local failure rate for 330 lobular carcinoma of breast cancer treated with breast-conserving therapy according to positive margin status for invasive carcinoma and age category.

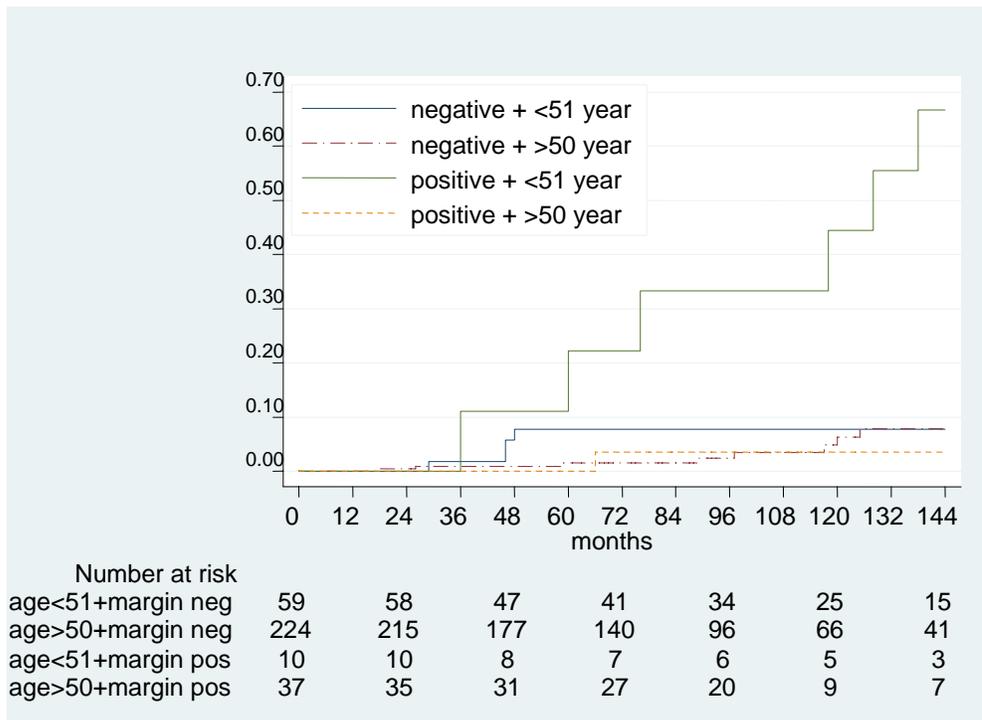


Fig. 2 The 12-year disease specific survival for 318 patients with lobular carcinoma for breast cancer and all treated with breast-conserving therapy according to differentiation grade.

