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Original Paper

Extensive and Predominant *In Situ* Component in Breast Carcinoma: their Influence on Treatment Results after Breast-conserving Therapy

H.P. Sinn,[1] H.W. Anton,[2] A. Magener,[1] D. von Fournier,[2] G. Bastert[3] and H.F. Otto[1]

[1]Department of Pathology, University of Heidelberg, Im Neuenheimer Feld 220, 69120 Heidelberg; [2]Department of Gynaecological Radiology; and [3]Department of Obstetrics and Gynaecology, University of Heidelberg, Voβstr. 9, 69115 Heidelberg, Germany

Intramammary tumour recurrence is one of the most important problems in breast-conserving therapy. We reviewed a series of 957 patients treated with breast-conserving therapy for primary invasive breast carcinomas between 1 January 1985 and 31 December 1992 at the University of Heidelberg. All histological slides were re-evaluated for risk factors with special emphasis on the extent and subclassification of the *in situ* tumour and the margin status. Six parameters were identified as significant risk factors for intramammary recurrence in the univariate analysis, including extensive or predominant *in situ* component (EIC, with at least twice the greatest dimension of the invasive tumour component), histological grade, angioinvasion, lobular tumour type, involved resection margin and lymph node status. The presence of an EIC was statistically correlated with low tumour grade, tumour at the resection margins and in re-excision specimens and with multifocal tumour invasion. Multivariate logistic regression analysis revealed that EIC (relative risk (RR) = 1.9), tumour grade (RR = 1.76), angioinvasion (RR = 1.34), lobular tumour type (RR = 1.65) and young age (≤ 40 years, RR = 1.39) were independent predictors of local recurrence. When combining these factors in a linear model, the simultaneous presence of at least two of the five risk factors predicted a 5-year risk of intramammary recurrence of 20.9% compared with a risk of only 1–5% when none or one of these risk factors were identifiable. We conclude that the risk of subsequent intramammary recurrence after breast-conserving therapy can be estimated from a scoring system that includes four histological risk factors and the patient's age. © **1998 Published by Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, breast-conserving therapy, local recurrence
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INTRODUCTION

BREAST-CONSERVING therapy (BCT) has become a standard therapy for locally resectable tumours since it was demonstrated to be as effective as modified radical mastectomy [1, 2]. Local tumour control can be achieved by tumour excision with histological clear margins and postoperative radiotherapy [3]. Nevertheless, the incidence of intramammary recurrences varies between 0.3 and 21% after 5 years of follow-up [4–12]. One of the most important issues is, therefore, the identification of the subgroup of patients who are at high risk for intramammary tumour recurrence. These local tumour recurrences are considered to be related to the histological characteristics of the primary tumour [5, 13–17], but it remains controversial which are the most important histological risk factors for local recurrence. This study was aimed at the detailed analysis of the histological risk factors, with special emphasis on the extent of the intraductal component. The non-invasive tumour component (intraductal or intralobular carcinoma) associated with invasive carcinomas, is one of the most often cited histological risk factors, but also the one most difficult to estimate. This *in situ* component (ISC) may vary greatly in size and occurs not only with invasive ductal carcinomas but can also be associated with almost any

Correspondence to H.P. Sinn.
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other histological tumour type. The evaluation of the extent, type and the relationship to the surgical margins of the intraductal component may be difficult in BCT specimens and the relevance of these factors for treatment decisions (re-excision, secondary mastectomy, radiotherapy) is not certain.

In this study we evaluated the known histological risk factors in a series of 957 patients treated for invasive breast carcinoma by BCT at our institution and compared these factors with the risk imposed by the non-invasive tumour component. This included the absolute and relative size (*in situ*: invasive tumour size) of the intraductal tumour component, its grade, subclassification and the relationship to the surgical margins. On the basis of these results we advocate the use of a systematic sampling method to evaluate the size of the intraductal component. This allows for a more precise estimation of the risk of subsequent intramammary tumour recurrence when used in conjunction with other independent risk factors.

PATIENTS AND METHODS

Patients

At the Department of Gynaecology of the University of Heidelberg, BCT has been performed systematically since 1975 as quadrantectomy or segmental resection in conjunction with adjuvant radiotherapy [18]. On the basis of earlier results that documented the importance of the lymphatic and intraductal tumour extensions [19], we chose to analyse all patients treated in the 8-year period between 1985 and 1992.

The main clinical and histological characteristics of these 957 patients are listed in Table 1. During that time, the policy at our institution was to manage breast carcinomas with a clinical or mammographic tumour diameter of less than or equal to 3 cm by BCT, if there were no surgical or oncological contra-indications (such as multicentricity). The surgical strategy was to resect the tumour by a wide local excision (segmentectomy) with operative margins of at least 1 cm and to re-excise the margins when doubtful or involved intraoperatively. The standard adjuvant irradiation schedule was whole breast irradiation with 50 Gy and an additional boost of 10 Gy to the tumour field. This was amended on an individual basis: 29 patients received between 30 and 45 Gy whole breast irradiation, another 17 patients received 60 Gy. No boost to the tumour field was administered in 48 cases. The time interval from surgical excision to radiotherapy was between 4 and 8 weeks. The policy for the administration of systemic therapy was $3 \times$ CMF or $6 \times$CMF for high risk and premenopausal patients and/or tamoxifen for postmenopausal patients.

As a rule, all specimens removed by segmentectomy were inked by the surgeon and marked topographically with sutures. When extensive calcifications were present, post-segmentectomy mammograms were performed to confirm the removal of all calcifications. The resection margins were not evaluated on frozen sections but only on paraffin sections. Cases with secondary mastectomy were excluded from the statistical analysis. Based on the results of paraffin histology, a re-excision was performed in 232 cases. After re-excision, the final resection margins were still involved or doubtful in 38 cases.

Follow-up information regarding vital and tumour status was available for all but 23 patients. Patient follow-up was received from the outpatient clinic and from consulting the physicians of the institution involved in the aftercare. The median follow-up time was 62.4 months (range 3.4–129.2 months).

Table 1. *Clinical and histological patient characteristics of all* 957 *patients treated with breast-conserving therapy*

	Patient numbers *n* (%)
Median age (range)	52.9 years (25–87)
Median tumour size (range)	1.8 cm (0.1–7.5)
pT category	
pT 1a	39 (4.1)
pT 1b	105 (11.0)
pT 1c	361 (37.7)
pT 2	397 (41.5)
pT 3	28 (2.9)
Not evaluable	27 (2.8)
Tumour type	
Invasive ductal carcinoma	707 (73.9)
Invasive lobular carcinoma	136 (14.2)
Tubular carcinoma	57 (6.0)
Mucinous carcinoma	22 (2.3)
Medullary carcinoma	27 (2.8)
Other invasive carcinoma	8 (0.8)
Grade of differentiation	
1	161 (16.8)
2	548 (57.3)
3	229 (23.9)
Not evaluable	19 (2.0)
Lymph node status	
Negative	588 (61.4)
1–3 positive nodes	174 (18.2)
4 or more positive nodes	121 (12.6)
No lymph node dissection	74 (7.7)

Histopathology

For the purpose of re-evaluation of the histological risk factors and the extent of the ISC all histological slides of the cases were retrieved from the files. Tumours were classified according to the WHO classification of breast tumours [20] and graded according to the modified Bloom and Richardson system proposed by Elston and Ellis [21].

The retrospective determination of the size of the ISC was possible because of our protocol of working up the specimens. This included the systematic and topographic sectioning of the specimen into 0.5 cm slices after 24 h fixation in 10% buffered formalin. These slices were numbered consecutively and the sections taken were additionally labelled according to their relative position and topography. This method permitted the retrospective evaluation of the relative sizes of both the invasive and the non-invasive components and their relationship to the surgical margins. The maximum diameter of the ISC was, therefore, estimated by dividing the number of slices containing the ISC (minus one) by the total number of tissue slices and multiplying the result by the maximum diameter of the specimen. This method is illustrated in Figure 1. The size of the invasive component was measured grossly or, if involving only one or two of the 0.5 cm slices, measured under the microscope using an ocular micrometer. In cases of multifocal or multicentric carcinomas, only the size of the largest invasive nodule was considered for tumour staging, in accordance with the TNM system of tumour classification [22]. The term 'multifocality' or 'multifocal invasion' was used when a tumour had multiple histologically identical nodules and an intervening intraductal

or lymphangic component. In contrast, we considered multicentricity only in those rare instances when independent tumours were present in the breast separated by 3–4 cm of uninvolved glandular tissue. There were no multicentric tumours among the 957 cases that underwent BCT.

Size was used for classifying the tumours into five different categories according to the relationship of the non-invasive carcinoma compared with the invasive carcinoma (see Table 2). We applied the terms extensive *in situ* component (EIC) or predominant *in situ* component (PIC) if the non-invasive component was at least two or four times larger than the invasive carcinoma, respectively (the latter definition is concordant with WHO terminology [20]). For statistical analysis, the cases with an EIC or a PIC were combined and compared with the tumours with no, small or intermediate ISCs. When the criteria of EIC or PIC were met, the size, growth pattern (comedo, solid, cribriform, micropapillary) [23, 24] and nuclear grade (on a three point scale) [25] of the ISC were recorded.

Other parameters recorded during reclassification included the presence of invasive or non-invasive tumour at resection margins, the minimum distance of invasive tumour to the resection margins, focal or massive angioinvasion and the presence of invasive or non-invasive tumour in re-excision specimens. Lymph node status was recorded as the number of nodes examined and in the case of lymph node metastases, the number of metastases, size, highest axillary level and pericapsular invasion.

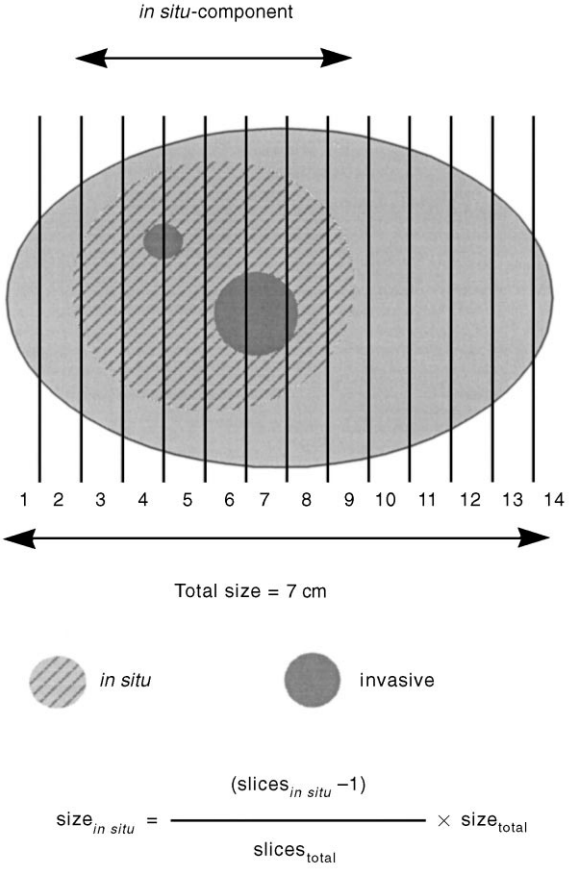

Figure 1. Method of systematic sampling of the tumour specimen for the estimation of the size of the *in situ* tumour component. In the example shown here, the size of the *in situ* carcinoma can be calculated as 3.5 cm.

Statistics

Our objective was to analyse the risk for any newly developing invasive or non-invasive carcinoma in the same breast, including 'true' recurrences and second primaries. Therefore, all instances of invasive or non-invasive mammary carcinoma occurring 4 months or later in the same breast were taken as intramammary recurrences (when primary therapy was considered to be completed). Only one 'recurrence' was observed earlier (after 120 days). All newly appearing invasive or non-invasive carcinomas within the same breast were regarded as intramammary recurrences, without regard to the tumour histology or the location within the breast. We did not exclude local recurrences that occurred after the detection of distant metastases from the analysis, as Gelman suggested [26], although both events may have risk factors in common but seem biologically independent. Classified values were tested using the two-sided χ^2-test or the Fisher's exact test for dichomotous variables. Continuous values were compared statistically by the Mann–Whitney rank-sum test. P values of 0.05 or less were considered statistically significant. For the univariate calculation of recurrence-free survival, the Kaplan–Meier estimator with the log-rank test was used [27]. 1 patient was excluded from the survival analysis because she refused radiotherapy. Results are given with two standard errors (SEM) (approximate 95% confidence interval (CI)). For multivariate estimation of the recurrence risk, parameters that were significant in the univariate statistics were re-coded 0 and 1 (0 = no risk, 1 = risk) and entered into the Cox proportional hazards regression analysis of risk factors. All calculations were performed with SPlus Ver. 3.3 (Mathsoft, Seattle, Washington, U.S.A.).

RESULTS

Relationship between invasive tumour and intraductal tumour components

Of the cases, 679 tumours (71%) were associated with a peritumoral ISC. Among these were 152 tumours (15.9%) that had an EIC or a PIC according to the definitions given above. These included 123 invasive ductal carcinomas (12.6%), 19 invasive lobular carcinomas (2.0%) and 10 tumours of other histological type (1.0%). The median invasive tumour size for tumours with no or a small ISC (2.0 and 1.7 cm, respectively) was significantly different compared with tumours with an EIC or a PIC (1.2 and 0.5 cm, respectively, $P < 0.001$). In contrast, the histologically evaluated size of the ISC was 3.0 and 3.5 cm (median values), respectively, for EIC and PIC cases (Figure 2).

Table 2. Definitions used for the attributes assigned to the size of the intraductal or intralobular (in situ) *tumour component in relation to the invasive tumour component and the number of patients receiving breast-conserving therapy as definitive therapy in each category*

Extent of the extratumoral *in situ* component	Size of extratumoral *in situ* component (ISC) and of the invasive tumour component (IVC)	No. of cases (%)
None	No ISC	278 (29.0)
Focal	ISC < IVC	527 (55.0)
Intermediate	ISC ≥ IVC, but < 2×	
Extensive	ISC ≥ 2× IVC but < 4×	98 (10.2)
Predominant	ISC ≥ 4 × IVC	54 (5.6)

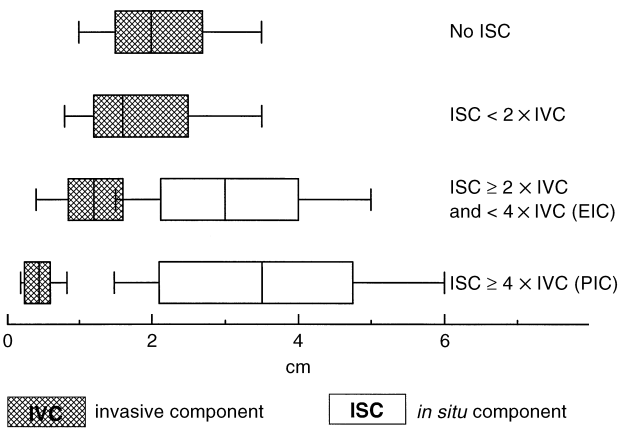

Figure 2. Box plot indicating the relationship of the *in situ* tumour component (ISC, open boxes) to the invasive component (IVC, hatched boxes). Error bars indicate the 10th and 90th percentiles, boxes indicate the 25th and 75th percentiles.

In order to analyse the relationship of the relative size of the intraductal component to other risk factors, the patients were analysed according to the extent of the intraductal component outlined in Table 2. For this purpose, the first three categories (none, focal or intermediate ISC) and the other two categories (EIC or PIC) were combined and compared with one another. Patient groups were not different with respect to age or menopausal status (Table 3). Also, no differences were observed with respect to bilateral breast carcinomas, the clinical tumour size or the expression of oestrogen or progesterone receptors (data not shown). The cases with an EIC or a PIC were similarly distributed among the histological tumour types, but carcinomas with an EIC or a PIC were only rarely rapidly proliferating tumours with poor differentiation. The presence of an EIC or a PIC was significantly associated with other factors which are adversely correlated with negative excision margins. Multifocal invasion was almost 10 times more frequent (32.2% versus 3.5%). Also, when an EIC or a PIC was present, margins of resection at primary operation were involved in more than 50% of all cases with invasive or intraductal carcinoma, similarly, invasive or non-invasive tumour was present in more than 25% of the re-excision specimens (Table 3).

Univariate analysis of risk factors for intramammary recurrence

After a median follow-up of 62.4 months, 57 of the 957 patients had developed an intramammary tumour recurrence. The calculated actuarial intramammary recurrence rate for all patients was $6.1 \pm 0.9\%$ (after 5 years ± S.E.), this includes, as stated in Materials and Methods, all invasive and non-invasive tumour recurrences in the same breast. The median tumour size of these recurrences was 1.8 cm (minimum 0.2 cm, maximum 6.0 cm). Among these recurrences were 9 cases of intraductal carcinoma, of which 8 had an invasive carcinoma with an EIC before. Five intramammary recurrences occurred after distant metastases were diagnosed. When comparing the group of patients aged 40 years or less at surgery with older patients, the 5-year actuarial local control rates were significantly different with $87.9 \pm 3.7\%$ versus $94.6 \pm 0.9\%$, respectively ($P = 0.003$) (Figure 3e). The presence or absence of oestrogen or progesterone receptors in the tumour was not related to local recurrence (not shown).

The actuarial local control rate for tumours 2 cm or smaller in diameter was $94.9 \pm 1.1\%$ and did not differ significantly from tumours measuring more than 2 cm in size ($92.4 \pm 1.5\%$). Also, no significant differences were found when the total tumour size (consisting of an invasive and an *in situ* component) was considered. In contrast, the proportion between the ISC and the invasive carcinoma was significantly related to the occurrence of local relapse. Patients with an ISC of at least twice the maximum diameter of the

Table 3. Comparison of clinical and histological parameters according to the extent of the extratumoral in situ *component (ISC). Continuous values* are given as the median value (range in parentheses), non-continuous values are stated as absolute figures (percentages in parentheses)*

	None, focal or moderate ISC ($n = 805$) (% or range)	Extensive or predominant ISC ($n = 152$) (% or range)	*P* value
Median age (range)*	53.3 (25–87)	51.6 (32–81)	NS
Premenopausal status	301 (37.4)	44 (28.9)	NS
Tumour type			
Invasive ductal	584 (72.5)	123 (80.9)	NS
Invasive lobular	117 (14.5)	19 (12.5)	
Other	104 (12.9)	10 (6.6)	
Histological grade 3	207 (25.7)	22 (14.5)	0.004
Histological size of invasive component (mm)*	20 (2–75)	10.5 (2–40)	< 0.0001
Multifocal invasion	28 (3.5)	49 (32.2)	< 0.0001
Presence of tumour at resection margin (at primary operation)			
Non-invasive tumour	50 (6.2)	70 (46.0)	< 0.0001
Invasive tumour	108 (13.4)	20 (13.2)	NS
Tumour in re-excision specimens at primary operation			
Non-invasive tumour	31 (3.9)	33 (21.7)	< 0.0001
Invasive tumour	58 (7.2)	19 (12.5)	NS

NS, not significant.

invasive carcinoma (EIC and PIC) had a 5-year recurrence-free survival of 85.2 ± 3.5% versus 95.6 ± 0.8% with a small or no ISC ($P < 0.001$, Figure 3a). Interestingly, this risk was significantly increased only when the ISC was of the comedo type (5-year recurrence-free survival 78.6 ± 8.6% versus 94.1 ± 4.0% for non-comedo type). Similar figures were calculated for nuclear grade 3 of the intraductal component. However, this was not an independent risk factor, as the nuclear grade of the ISC was highly correlated with the grade of the invasive component.

Another, but less significant, factor was the presence of invasive carcinoma at the primary resection margin and the

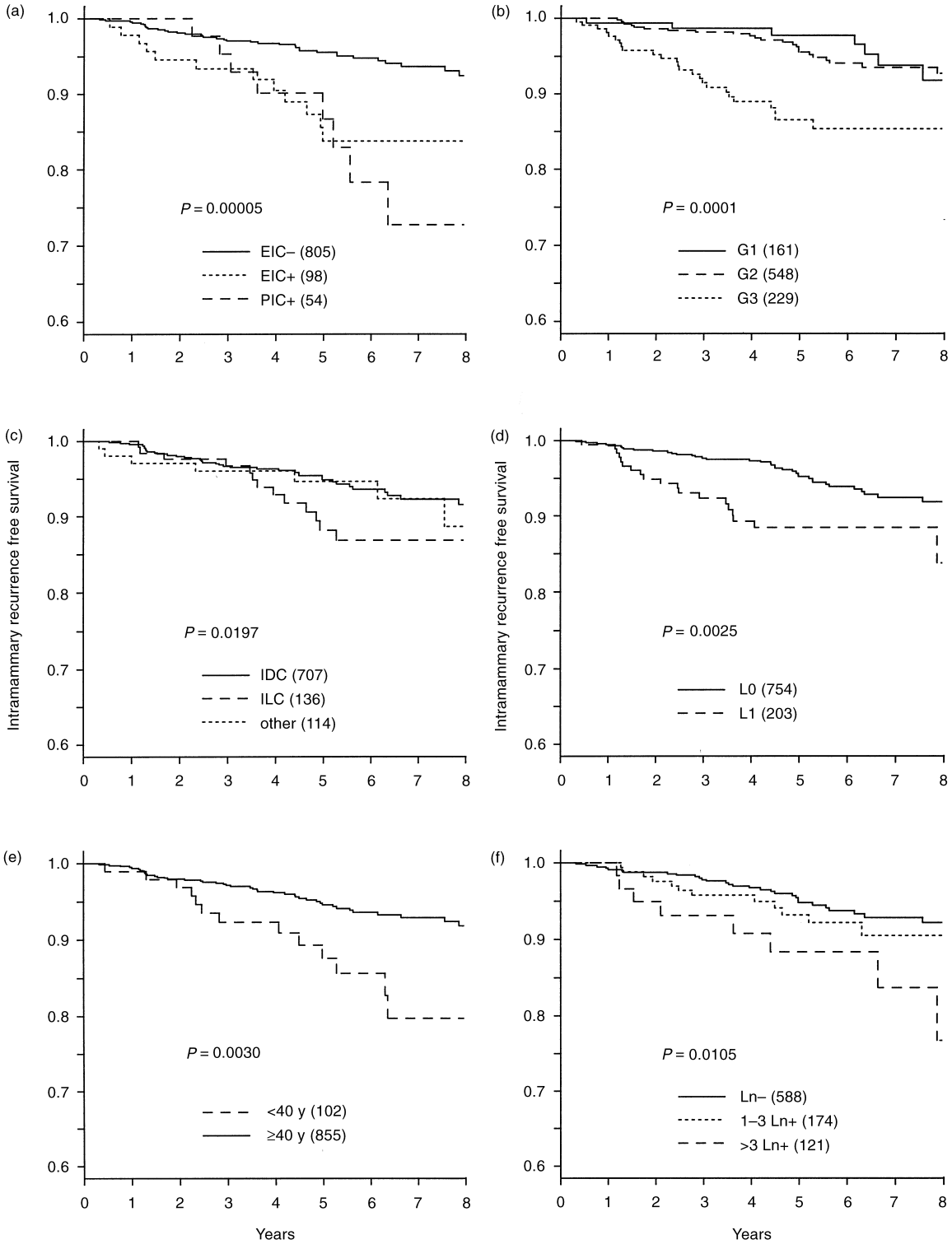

Figure 3. Univariate analysis of 8-year intramammary recurrence-free survival curves for six independent risk factors: (a) extensive or predominant intraductal component; (b) histological tumour grading; (c) tumour type; (d) angioinvasion; (e) age; and (f) lymph node status.

minimal distance to the margins. A good 5-year local control rate of 97.6 ± 4.2% was obtained with a measured distance of 3 mm or more, compared with 93.0 ± 8.3% with close margins (1–2 mm) and 85.2% ± 9.3% with tumour within the resection margin. When analysing the significance of involved or doubtful definitive margins by invasive or intraductal carcinoma ($n = 165$), a smaller but significant increase in risk was observed (89.6 ± 2.3 versus 95.2 ± 0.9%, $P = 0.01$).

Another adverse factor for intramammary tumour recurrence was the lobular tumour type. Invasive ductal carcinoma and other tumour types (tubular, medullary, mucinous and papillary carcinomas) behaved nearly identically with an actuarial 5-year local control rate of 94.8 ± 0.8% compared with 88.2 ± 3.3% for invasive lobular carcinoma. This difference between invasive lobular carcinomas and other tumour types was significantly different ($P = 0.0197$), but the recurrence rates became discrepant after only 3 years (Figure 3c). Three other histological parameters that had a significant influence on local relapse were tumour grade, nodal status and angioinvasion. Grade 1 and 2 carcinomas were very similar in 5-year recurrence-free survival rates of 97.8 ± 1.2% and 95.5 ± 1.0%, but for grade 3 carcinomas it was 86.5 ± 2.6% ($P < 0.001$, Figure 3b). The axillary lymph node status highly correlated statistically with angioinvasion (L1 category), and both parameters were also very good predictors of intramammary recurrence (Figure 3d). Interestingly, tumours with a negative nodal status behaved similarly to tumours with a maximum of three positive axillary nodes with 5-year recurrence-free survival of 94.8 ± +1.0% and 93.3 ± 2.1% compared with 88.3 ± 4.5% in tumours with more than three axillary lymph node metastases (Figure 3f). Very similar values were calculated for tumours with metastases in axillary level 1 only when compared with tumours with metastases in level 2 or 3 (not shown).

Multivariate analysis of intramammary recurrence

All parameters that were significant in the univariate analysis of risk factors were entered into the Cox model of logistic regression analysis. However, lymph node status was first not included in order to put the emphasis on local risk factors. Only five parameters, namely the relative extent of the ISC, histological grade, angioinvasion, the tumour type and the patient's age emerged as independent factors. The relative risk ratio varied between 1.9 for the EIC and 1.39 for age ≤ 40 years (Table 4). When lymph node status was included in the analysis, the result was almost identical, but the number of lymph node metastases replaced the parameter angioinvasion. The involvement of the definitive surgical resection margins by invasive or intraductal carcinoma lost its significance in this multivariate model, presumably as it is confounded by the EIC or other morphological factors. The resection margin was also not a significant factor when two separate statistical models were constructed for the presence and absence of the EIC.

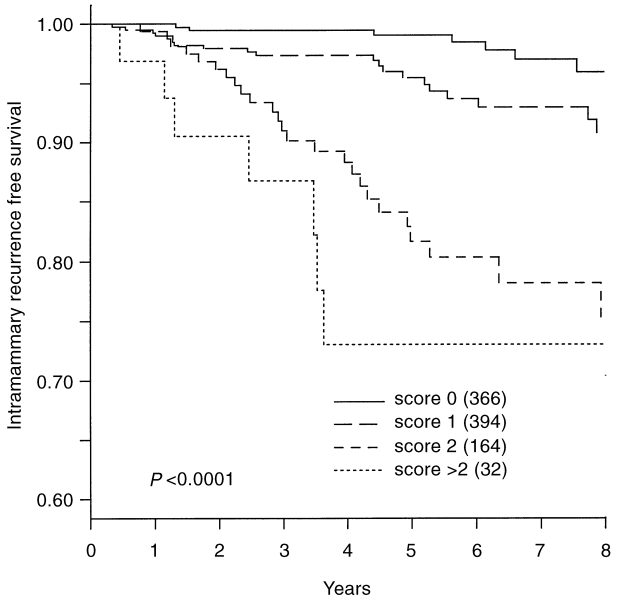

Figure 4. Intramammary recurrence-free survival curves comparing the linear combination of the risk factors significant in the multivariate analysis.

In order to estimate the individual risk of tumour recurrence based on these risk factors, a linear model was constructed. This consisted of a risk score that attributed one point for any of the five independent risk factors. This risk score turned out to be most useful in assessing the risk for intramammary tumour recurrence. When none of these risk factors was present, the intramammary recurrence-free survival was 99.0 ± 0.6%, compared with 95.4 ± 1.2% with any one of the risk factors and 79.1 ± 3.6% with two or more risk factors (Figure 4).

DISCUSSION

Breast carcinomas of all major histological subtypes can be associated with a non-invasive (*in situ*) tumour component that may exceed the invasive carcinoma several times in size. We have shown here that the ISC is the single most important factor for the risk of intramammary tumour recurrence, provided that strict attention is paid to the margin status, as it was in this case series where re-excisions were performed in 232 out of the 952 cases. However, it is apparently neither the presence nor the absolute size of this tumour component that is associated with an increased risk, but the relationship between the invasive and the non-invasive tumour components. Therefore, the success of BCT strategies primarily depends on this and other histological factors that can be determined

Table 4. *Multivariate logistic Cox regression analysis of prognostic factors for intramammary tumour recurrence*

	Adverse factor	No. at risk	Risk ratio	95% CI	*P* value
1. *In situ* component	ISC $\geq 2 \times$ IVC	152	1.90	1.38-2.44	7.7×10^{-6}
2. Histological grade	Grade 3	229	1.76	1.32-2.32	7.2×10^{-5}
3. Histological type	ILC	136	1.65	1.20-2.21	0.001
4. Angioinvasion	Present	203	1.34	1.00-1.77	0.043
5. Age	< 40 years	102	1.39	1.02-1.94	0.046

ISC, *in situ* component; IVC, invasive tumour component; ILC, invasive lobular carcinoma.

by the careful examination of the surgical specimen. The association between the extent of the intraductal component and the increased risk of intramammary recurrence was first noted by Schnitt and colleagues [28] and shown by Holland and associates [29] to be due to residual intraductal tumour foci after BCT. The Boston group subsequently defined the EIC as intraductal carcinoma present in more than 25% of the tumour area and also in adjacent normal breast tissue [30, 31]. When applying this definition, the percentage of tumours with an EIC varied between 12 and 38% [13, 14, 28, 32, 33]. It must be emphasised however, that this definition does not take into account the size of the peritumoral intraductal tumour extension. The Amsterdam group defined the EIC as 10 or more involved ducts outside the invasive tumour [34]. Our approach is different still and we have based the definition of the EIC on the relationship of the size of the intraductal component to the size of the invasive tumour. This definition of the EIC (the non-invasive component exceeding the invasive carcinoma by at least twice) is relatively strict, and only 15% of cases fulfilled this criteria. This definition also includes invasive ductal carcinomas with a predominant intraductal component, as defined by the WHO to be at least four times the size of the invasive tumour component. In this way, the term EIC can be applied to histological tumour types other than invasive ductal carcinoma. In this series, the proportion of ductal, lobular and other tumour types having an EIC was similar. Therefore, it appears useful to assess the intraductal component with all types of breast carcinomas.

It has been shown previously that the EIC is statistically associated with other adverse risk factors, such as unsatisfactory resection margins, histological grade 3 and multifocality [8, 15, 35–38]. It was speculated that this could explain the higher rate of intramammary tumour recurrences in young patients. In fact, our data support this assumption because, in the multivariate analysis, the EIC and the histological grade emerged as the most important and significant risk factors, while patient age was ranked as the least important parameter and the margin status lost its significance. Therefore, young age is not among the most important risk factors for intramammary tumour recurrence [15, 36, 39]. One possible reason for age being an independent risk factor in this analysis might be that we have counted all newly developed carcinomas (true recurrences and second primaries) within the same breast as intramammary recurrences. The greater possibility of developing a second primary in young patients could have increased the risk of 'local recurrence'.

Because of the importance of the extent of the extratumoral non-invasive component, should this tumour component be included in the measurement of the total tumour size? The term 'tumour size', or the corresponding pT category of the TNM system, is used to indicate the size of the invasive tumour only. This parameter is, therefore, useful as an estimate of metastatic risk, but not to select patients who are suitable for BCT. Therefore, in this and also in previous studies, the invasive tumour size or the pT category had no influence on intramammary recurrence after BCT [5, 9, 12, 31]. Even with tumours of 4 cm and larger the 5-year intramammary recurrence rate was calculated as 8.5% [40]. Because of these considerations, we have attempted to measure the ISC and the invasive tumour component separately and to correlate these with the risk of local failure. It was anticipated that the total tumour size (consisting of both the intraductal and the invasive tumour component) would be a useful predictor of intramammary tumour recurrence. However, the data which have been presented here show that, in fact, the best predictor for intramammary recurrence is the relative proportion of the invasive component to the ISC. The most likely explanation for this finding would be that this ratio reflects the probability of underestimating the intraductal tumour component intra-operatively and the inadequate tumour excision. To illustrate this, a carcinoma with a 1 cm intraductal component outside a 2 cm invasive tumour would more likely be treated by a wider excision than another carcinoma of 3 cm total size, but with a 0.5 cm invasive component in its centre, as the first tumour is easier to palpate intra-operatively. Neither the pT category nor the size of the invasive tumour component was a risk factor in univariate or multivariate analysis of the intramammary recurrence, probably for these reasons. Interestingly, our results also confirm the assumption that the EIC behaves more aggressively when consisting of ductal carcinoma *in situ* (DCIS) of comedo subtype and of poor nuclear grade. This is compatible with reported results from other investigators concerning the recurrence risk of pure DCIS following BCT [25, 41].

Some risk factors that were associated with local tumour recurrence in our analysis were also responsible for increased risk of distant treatment failure, namely young age, high tumour grade and angioinvasion. Therefore, some patients with these risk factors may get distant metastasis and die before a local recurrence would evolve. Because of this consideration, some prognostic factors, such as tumour grade and angioinvasion, may have been underestimated in the analysis of risk factors for intramammary tumour recurrence and actually play a more important role than can be statistically validated.

In conclusion, it emerged from our analysis that only four histological criteria and patient age are responsible for the risk of intramammary tumour recurrence after multivariate analysis of risk factors. By combining these factors, it is possible to define a patient population at risk of local recurrence after BCT using a limited set of parameters. This combination of risk factors permits the prospective identification of patients at high risk for tumour recurrence.

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