What modifies the relation between tumour size and lymph node metastases in T1 breast carcinomas?

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Abstract

***Aims*—To evaluate which pathological and clinical parameters modify the relation between tumour size and lymph node metastases in invasive breast carcinomas < 20 mm.**

***Methods*—In a retrospective study, 1075 patients with pT1 invasive breast carcinoma and with known nodal status were analysed. The size of the infiltrating tumour was microscopically evaluated, and the in situ component was not considered. The additional pathological parameters considered were: tumour grade, peritumoral vascular invasion, multicentricity, and angiogenesis. The immunophenotype of the tumour was determined as: the expression of oestrogen (ER) and progesterone (PR) receptors, p53, and c-erbB2. The patients were grouped by age as follows: < 50, 51–70, and > 70 years old.**

***Results*—Three hundred and seventy four patients (34.8%) were node positive. Univariate analysis showed that nodal positivity was significantly correlated with large tumour size (> 10 mm), vascular invasion, grade 2–3, multicentricity, and high angiogenesis (> 100 microvessels/×20 high power frame). No significant correlation was found between nodal positivity and ER, PR, p53, or c-erbB2 status. Interestingly, the association with in situ carcinoma was correlated with lower nodal positivity in tumours presenting equally sized infiltrating components. Age was an independent variable and significantly modified the risk of nodal positivity in tumours < 1 cm. In fact, in patients under 51 years of age, the proportion of nodal positivity in pT1a tumours was sevenfold higher than in older patients. In patients from 51 to 70 years old, nodal positivity correlated with tumour size, and multicentricity was an additional risk factor.**

***Conclusions*—These data suggest that, together with tumour size, the presence of in situ carcinoma, and vascular invasion, age is one of the most important predictors of metastatic diffusion in breast carcinomas.**

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It is well known that the presence of lymph node metastases in breast carcinoma is directly proportional to tumour size. Mammographic screening, which allowed the early detection of breast carcinomas with a low risk of lymph node metastases, prompted a series of studies that debated the usefulness of axillary lymph node dissection. Although a classic and important staging procedure in the treatment of breast cancer,[1] because of its high morbidity,[2] axillary lymph node dissection tends to be avoided in small tumours where the expected incidence of node metastases is low.[3–6]

However, the reported frequency of lymph node metastases associated with small tumours is too variable to rule out axillary dissection altogether. This variability might have several causes, such as the poor reproducibility of the measurement of small invasive carcinomas, and the need to examine a sufficient number of lymph nodes to obtain reliable results.

In addition to these two possible methodological biases, there are other clinical and pathological factors that might influence the nodal status in breast cancer. Age has been shown to be an important predicting factor; in fact, lymph node metastases decrease with increasing age,[7] and a recent study has shown that elderly women are less frequently treated with axillary dissection than younger patients.[8] Instead, although breast carcinoma is rare in women 35 years of age or younger, the reported incidence of lymph node metastases reaches 59% overall and 27.6% in T1 breast carcinomas.[9]

Other studies evaluated the influence of various morphological factors such as tumour histotype, grade, and vascular invasion on the presence of lymph node metastases in small invasive breast carcinomas. Barth *et al* concluded that the independent predictors of metastases are lymph/vascular invasion, tumour palpability, nuclear grade, and tumour size.[10] Recently, Maibenco *et al* found that only very small carcinomas of special types (tubular, papillary, and mucinous) are associated with a low frequency of lymph node metastases (< 5%).[7]

The recent introduction of the sentinel lymph node procedure has already reduced the number of unnecessary lymphadenectomies.[11 12] However, some patients will require chemotherapy even though the sentinel lymph node is negative. The information provided by the histology of the sentinel lymph node, together with the evaluation of the specific tumour phenotype and the clinical features of each single patient, need to be considered for the provision of individualised treatment.

To provide this information, in this retrospective study we evaluated the correlation between tumour size and lymph node status in a series of 1075 pT1 breast carcinomas in which the tumour dimension and the number of lymph nodes were determined using standardised procedures. In addition, we evaluated how patient age and other pathological parameters modify the linear relation between tumour size and lymph node metastases.

Materials and methods

We studied 1075 consecutive patients with pT1 invasive breast carcinoma who underwent total axillary dissection between 1995 and 1998. None of the patients was submitted to the sentinel lymph node procedure. Special care was taken to determine the tumour size and to evaluate the lymph node status.

Palpable tumours were cut along their major diameter and measured. Because all the lesions examined were < 2 cm, it was possible to obtain one tissue block representing the largest diameter of the tumour on the cutting section. In this way, the gross evaluation of tumour size was always microscopically confirmed, thereby excluding possible bias as a result of the presence of a peripheral in situ carcinoma. The difference in tumour size between fixed and fresh tissues was irrelevant. Non-palpable lesions were identified by a hook wire or a staining solution placed under ultrasonographic or mammographic control before surgery. When suspicious calcifications were the cause of the biopsy, the surgical specimen was sliced and then radiographed using faxitron, and tissue embedding was focused on the sections containing the calcifications. In non-palpable lesions, tumour size was microscopically measured and the largest diameter of the invasive component was reported.

When the invasive carcinoma (IC) was associated with peripheral ductal in situ carcinoma (DCIS), the size of the two lesions was reported separately, according to the instructions given by the European guidelines,[13] and only the IC was considered for tumour staging. Tumours were categorised using the last edition of the TNM system of the American Joint Committee on Cancer.[14] ICs were classified as microinvasive Tmic, ⩽ 1 mm; T1a, ⩽ 5 mm; T1b, 6–10 mm; and T1c, 11–20 mm.

The axillary lymph nodes were sectioned through the hilum before formalin fixation. The residual adipose tissue was fixed overnight in Bouin's fluid, and than step sectioning was performed at 2–3 mm intervals. One to five sections for each block were examined after haematoxylin and eosin staining.

When the tumour was large enough to count mitoses under a ×10 high power field, it was graded according to the Elston and Ellis system.[15] Otherwise, the Bloom and Richardson grading system[16] was adopted. Peritumoral vascular invasion was evaluated morphologically on haematoxylin and eosin stained sections. Multicentricity, or multiple tumour foci, were reported only when they matched the criteria defined by the European guidelines,[13] such as the presence of two or more distinct tumour foci at a minimum distance of 4 cm, and/or in different quadrants. Multiple foci of invasive carcinoma within DCIS were measured as a single tumour mass and staged accordingly.[13]

In addition, the immunocytochemical expression of the following parameters was evaluated: oestrogen (ER) and progesterone (PR) receptor status (ERICA and PgICA; Abbot Diagnostica, Deikenheim, Germany), p53 (pooled 12-1; Histoline Biogenesis, Poole, Dorset, UK), and c-erbB2 (c-erbB2; Dako, Glostrup, Denmark). Angiogenesis was studied using CD31 (endothelial cell CD31; clone JC/70A, Dako) as an endothelial marker, and it was determined by counting at a magnification of ×20 in the area richest in blood vessels. Positivity of immunohistochemical staining was determined according to the suggested protocol deriving from the consensus report of the task force for basic research of the EORTC-GCCG.[17] Cut off values for positivity were established as follows: ER, 40%; PR, 50%; c-erbB2, 30% (only membrane staining was considered); and p53, 25%. The cut off point for angiogenesis was considered to be 100 positive vessels/×20 magnification field.

All the cut off values were calculated over the entire population, with expected normal quantiles calculated using Van der Waerden's proportional estimation formula, and assigning the mean to ties (detrended normal Q-Q plot). The results obtained almost overlapped with the lowest point of the bimodal distribution of value.[18]

The patients were grouped by age as follows: < 50 years, 51–70 years, and > 70 years. In most patients > 70 years, lymphadenectomy was performed only when the axillary lymph nodes were clinically palpable; therefore, this group was not considered in the analysis.

The χ^2 test for association and discriminant analysis with forward inclusion (Wilk's method; cut off values, 3.84 and 2.71) were used for univariate and multivariate analysis using SPSS for Windows (V 8.0).

Results

Axillary metastatic lymph nodes were found in 374 of 1075 patients (34.8%). The number of lymph nodes recovered from all specimens ranged from 10 to 25.

Tumour size was related directly to nodal positivity (table 1). In 199 cases, IC was associated with extensive peripheral DCIS. In all these cases the nuclear grade of DCIS was analogous to the grade of IC. The amount of DCIS in the whole tumour mass increased significantly as the IC size decreased. Microinvasive carcinomas were found within DCIS only,

Table 1 Relation between node positivity and tumour size

Tumour size	*Number of cases*	*Node positive (%)*
pT mic	14	0
pT1a	36	4 (11)
pT1b	172	30 (17.4)
pT1c (10–15 mm)	481	166 (34.5)
pT1c (>15 mm)	372	173 (46.5)

Table 2 Relation between node positivity and tumour size in patients without associated ductal carcinoma in situ

Tumour size	*Number of cases*	*Node positive (%)*
pT mic	0	0
pT1a	23	3 (13)
pT1b	128	23 (18)
pT1c (10–15 mm)	395	140 (35.4)
pT1c (>15 mm)	302	136 (45)

Table 3 Relation between node positivity and tumour size in patients with associated ductal carcinoma in situ

Tumour size	*Number of cases*	*Node positive (%)*
pT mic	14	0
pT1a	13	1 (7.6)
pT1b	44	7 (15.9)
pT1c (10–15 mm)	86	26 (30.2)
pT1c (>15 mm)	70	37 (52.9)

and none of them gave rise to metastases. Cases of IC T1a associated with DCIS were less frequently node positive than ICs of the same size without peripheral DCIS (tables 2 and 3).

Nine cases of extensive high nuclear grade DCIS of the comedo type with more than three foci of stromal invasion were identified in patients < 50 years old. In these cases, the incidence of nodal positivity was > 50%, and in two cases node positivity was accompanied by invasion of perinodal adipose tissue.

Univariate analysis of the entire population showed that nodal positivity was significantly correlated with tumour size, presence of vascular invasion, high nuclear grade (grades 2–3), multicentricity, and high angiogenesis (table 4). Within the different age groups, angiogenesis was higher in tumours with vascular invasion and in larger tumours. Furthermore, the CD31 count was a weak predictor of nodal positivity in pT1a and pT1b tumours, but it gained considerable importance in pT1c tumours.

The cut off point of tumour grading was set between grade 1 and higher grades, owing to the similar risk of nodal positivity in grade 2 and grade 3 tumours in the entire series. Grade 1 tumours were more numerous in pT1a and pT1b (49%) than in pT1c tumours (22%). Grade 1 tumours had a lower incidence of nodal positivity. After excluding grade 1 tubular and lobular carcinomas, grade lost its prognostic value. In grade 2 tumours < 1 cm, the percentage of node positivity was significantly lower than in G2 pT1c tumours (11% *v* 37%).

With multivariate analysis, tumour size, vascular invasion, and multicentricity were independent variables positively related to nodal positivity ($\chi^2 = 111.8$; $p < 0.0001$).

ER, PR, p53, and c-erbB2 expression showed no significant differences between the node negative and node positive groups.

Table 4 Relation between node positivity (N+) and different tumour pathological parameters in the 1075 patients

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Vascular invasion	291/614 (47.4%)	82/461 (17.8%)	4.1 (3.1 to 5.5)
Grades 2–3	307/779 (39.4%)	66/292 (22.6%)	2.2 (1.6 to 3.0)
Multicentricity	35/67 (52.2%)	338/1008 (33.5%)	2.1 (1.3 to 3.5)
CD31 >100 vessels/×20 field	145/360 (40.3%)	173/545 (31.7%)	1.4 (1.1 to 1.9)

CI, confidence interval; RR, relative risk.

Table 5 Relation between node positivity and tumour size in patients < 50 years of age

Tumour size	*Number of cases*	*Node positive (%)*
pT mic	7	0
pT1a	7	3 (42.8%)
pT1b	52	11 (21.2%)
pT1c (10–15 mm)	138	51 (37%)
pT1c (>15 mm)	118	65 (55.1%)

AGE

The patients were grouped by age as follows: < 50 years, 322 patients; 51–70 years, 610 patients; and > 70 years, 142 patients. The rate of nodal positivity was significantly higher in patients < 50 years than in those 50–70 years old (40.4% *v* 30.8 %; relative risk (RR), 1.5). The elderly patients (> 70 years) were not comparable with the other two groups, because in most cases lymphadenectomy was performed only when the axillary lymph nodes were clinically palpable.

Age group < 50 years

In this age group, nodal positivity was found in 40.4 % of cases (130 of 322). The linear relation between tumour size and nodal positivity was maintained (table 5). Univariate analysis showed that nodal positivity significantly correlated with tumours > 10 mm, vascular invasion, and high tumour grade (table 6). Multicentricity did not correlate with node positivity because of the small number of multicentric lesions in this group of patients. There were 298 unicentric tumours (38.9% node positive) and only 34 multicentric tumours (52.9% node positive).

Univariate analysis showed that in patients < 50 years old with small tumours (< 10 mm), node positivity was significantly correlated with vascular invasion. In fact, 33% of such cases (10 of 30) with vascular invasion were node positive compared with 10.8% (four of 37) of tumours without vascular invasion (RR, 4.1; confidence interval (CI), 1.1–7.5).

The number of CD31 stained vessels (97 ± 35) was high but not significantly related to nodal positivity.

In pT1c tumours, axillary positivity was related to: tumour size (11–15 mm *v* 16–20 mm), vascular invasion, and grade (table 7). In this subgroup of patients, multivariate analysis showed that tumour size and vascular invasion were the independent variables for node positivity ($\chi^2 = 38.8$; $p < 0.0001$).

Age group 51–70 years

In this group of patients, nodal positivity was 30.8% (188 of 610) and increased as the size of the IC increased (table 8). Univariate analysis showed that nodal positivity significantly correlated with tumour size, vascular invasion, high grade, multicentricity, and a trend for angiogenesis (table 9). CD31 counts (87 ± 37) in this group of patients were significantly lower than in younger women ($p < 0.001$).

Of 134 tumours < 10 mm, 18 were node positive (13.4%). Univariate analysis showed that node positivity was significantly higher in tumours with vascular invasion (26.3%) than in those without (8.4%): RR, 3.8; CI, 1.4 to

Table 6 Relation between node positivity (N+) and different tumour pathological parameters in patients < 50 years of age

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Tumour size >10 mm	116/255 (45.5%)	14/67 (20.9%)	3.1 (1.7 to 6.0)
Vascular invasion	103/202 (51.0%)	27/120 (22.5%)	3.6 (2.1 to 6.0)
Grades 2–3	108/248 (43.5%)	22/73 (30.1%)	1.8 (1.02 to 3.1)

CI, confidence interval; RR, relative risk.

Table 7 Relation between node positivity (N+) and different tumour pathological parameters in pT1c tumours in patients < 50 years

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Tumour size >15 mm	65/118 (55.1%)	51/138 (37.0%)	2.1 (1.3 to 3.5)
Vascular invasion	93/172 (54.1%)	23/84 (27.1%)	3.1 (1.7 to 5,5)
Grades 2–3	96/198 (48.5%)	20/57 (35.1%)	1.7 (0.95 to 3.2)

CI, confidence interval; RR, risk ratio.

Table 8 Relation between node positivity and tumour size in patients 51–70 years of age

Tumour size	*Number of cases*	*Node positive (%)*
pT mic	6	0
pT1a	23	1 (4.3%)
pT1b	104	17 (16.3%)
pT1c (10–15 mm)	278	87 (31.3%)
pT1c (>15 mm)	199	83 (41.7%)

10.1. With regard to tumour grade, a higher proportion of pT1a and pT1b tumours were grade 1 (49%) than were pT1c tumours (22%). Grade 1 tumours had a lower incidence of nodal positivity.

In pT1c nodal positivity was related to tumour size (11–15 mm *v* 16–20 mm), vascular invasion, grades 2 and 3, and multicentricity. A trend for angiogenesis was also found (table 10).

Table 9 Relation between node positivity (N+) and different tumour pathological parameters in patients 51–70 years of age

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Tumour size >10 mm	169/477 (35.4%)	18/133 (13.5%)	3.4 (2.0 to 5.9)
Vascular invasion	143/335 (42.7%)	44/275 (16%)	3.9 (2.65 to 5.7)
Grade 2–3	152/436 (34.9%)	35/172 (20.3%)	2.1 (1.4 to 3.2)
Multicentricity	16/29 (55.2%)	171/581 (29.4%)	2.9 (1.4 to 6.2)
CD31 >100 vessels/×20 field	67/185 (36.2%)	89/316 (28.2%)	1.4 (0.98 to 2.1)

CI, confidence interval; RR, risk ratio.

Table 10 Relation between node positivity (N+) and different tumour pathological parameters in pT1c tumours in patients 51–70 years of age

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Tumour size >15 mm	82/199 (41.2%)	87/278 (31.3%)	1.5 (1.1 to 2.2)
Vascular invasion	133/297 (44.8%)	36/180 (20%)	3.2 (2.1 to 5)
Grades 2–3	143/369 (38.8%)	26/107 (24.3%)	2.0 (1.2 to 3.2)
Multicentricity	16/25 (64%)	153/452 (33.8%)	3.4 (1.5 to 8.0)
CD31>100 vessels/×20 field	62/157 (39,5%)	79/244 (32.4%)	1.3 (0.9 to 2.0)

CI, confidence interval; RR, relative risk.

Table 11 Relation between node positivity (N+) and different tumour pathological parameters in patients > 70 years of age

Examined parameters	*N+/presence of parameter (%)*	*N+/absence of parameter (%)*	*RR (CI)*
Tumour size >10 mm	54/120 (45%)	2/23 (8.7%)	8.5 (1.9 to 38.3)
Vascular invasion	45/77 (58.4%)	11/66 (16.7%)	7.0 (3.2 to 15.5)
Grades 2–3	47/95 (49.5%)	9/47 (19.1%)	4.1 (1.8 to 9.5)
CD31 >100 vessels/×20 field	23/41 (56.1%)	28/82 (34.1%)	2.4 (1.1 to 5.3)

CI, confidence interval; RR, relative risk.

In multivariate analysis, vascular invasion and multicentricity were the independent variables ($\chi^2 = 38.3$; $p < 0.0001$).

Patient group > 70 years

In this group, lymphadenectomy was performed only when lymph nodes were clinically evident. This explains the high percentage (39.2%) of node positivity (56 of 143). Univariate analysis showed that nodal positivity significantly correlated with tumour size, vascular invasion, grade, and angiogenesis (table 11). Multivariate analysis selected vascular invasion as the variable independently related to axillary positivity ($\chi^2 = 23.4$; $p < 0.0001$).

Discussion

In this study of 1075 cases of breast carcinoma we confirmed that tumour size remains an important predictor of axillary lymph node metastases in breast carcinomas. However, we showed that other factors such as age, grade, vascular invasion, and angiogenesis can modulate the impact of tumour size on metastatic spreading.

Contrasting data have been published previously on the incidence of axillary lymph node metastases according to tumour size.[3 4 6 19] These discrepancies have been attributed to the different series analysed and to the different methods used to evaluate tumour size.

In our study, the lesions were sampled so that we always obtained at least one microscopic section reproducing the largest tumour diameter. In a recent study on axillary lymph node metastases in small invasive breast carcinomas, Maibenco *et al* discussed, among the limitations of their study, the lack of standardisation of tumour size measurement.[7] This limitation was bypassed in our work by using microscopic measurement only of the tumour diameter. This allowed us to limit our measurement to the invasive component of each tumour, and to exclude the associated peripheral in situ component, or to evaluate the exact dimension of the invasive carcinoma in predominantly in situ carcinomas. In a previous study, Seidman and co-workers demonstrated that this kind of tumour size measurement is a better predictor of lymph node status than the total tumour size.[20]

Interestingly, in a small number of pT1a tumours, we found that association with DCIS greatly reduced the risk of nodal positivity and that microinvasive carcinomas, all found associated with DCIS, were always node negative. This suggests that invasively borne tumours are more aggressive than tumours originating from in situ lesions.

Following the European guidelines[13] for multicentricity, we showed that tumours presenting with widely separate foci (at least 4 cm) are more frequently associated with node metastases. In fact, in women > 50 years of age multicentricity is an independent prognostic parameter of nodal involvement. The situation is probably similar in younger patients, but because of the small number of multicentric

lesions in this subgroup the results were not significant.

With regard to grade, in this series, grade 2 and 3 tumours were associated with an increased risk of node metastases, and this trend was maintained in all age subgroups. Nevertheless, this grouping strategy can introduce a falsely low risk calculation in patients > 50 years with a small tumour. In this age group, the node positivity risks are equally low in grade 1 (13%) and grade 2 (11%) tumours.

It has already been stated that vascular invasion is one of the most reliable predictors of node metastases.[10] In accordance with these previous observations, we found that the presence of vascular invasion is an independent predictor of node involvement.

Recently, it has been reported that vascular grading for angiogenesis significantly predicts node status.[21] Our data show that angiogenesis, evaluated as numbers of CD31 positive endothelial cells, is related to age and tumour size. Indeed, CD31 counts are higher in younger patients (97 ± 35 in patients $\leqslant 50$ years old; 87 ± 37 in older patients; $p < 0.001$) and, within the different age groups, are higher in the presence of vascular invasion and larger tumours. In fact, the CD31 count is a weak predictor of nodal positivity in pT1a and pT1b tumours, but it gains considerable significance in pT1c tumours. In younger patients, hormonal factors and/or the higher concentrations of circulating growth factors might upregulate angiogenesis, and in these patients angiogenetic activity is likely to be one of the most striking factors related to higher lymph node positivity

In our study, we found that age can influence the node status independently of tumour size. In fact, even very small tumours (pT1a) can frequently be associated with node metastases in young women (42.8% *v* 4.3% in older patients) (tables 5 and 8). In addition to these observations on pT1a carcinomas, we found that, in patients < 51 years old, tumours up to 10 mm have a threefold increased risk of node metastases than in older women. Therefore, lower age should be considered an independent prognostic indicator of node metastases, even in small breast cancers. Our data agree with reports by Maibenco *et al* that increasing patient age is associated with a progressively decreasing frequency of lymph node metastases.[7]

In our study, patients over 70 years of age were submitted to axillary dissection only when lymph nodes were palpable. This explains the high percentage of nodal positivity in this subgroup. The evaluation of tumour pathological parameters (tumour size, vascular invasion, multicentricity, and grade) might be useful for selecting a subgroup of older patients requiring more aggressive treatment.

In conclusion, our data indicate that although tumour size remains an important predictor of node metastases in breast cancer, there are at least two different variables that can affect its reliability. The first one is young age, which negatively influences the clinical behaviour of very small breast carcinomas. The second one is the association of invasive carcinoma with an in situ component, which surprisingly seems to reduce the risk of node metastases in tumours with an equally sized invasive component. Thus, precise microscopic measurement of invasive carcinomas and the evaluation of their association with DCIS is imperative if correct tumour staging is to be obtained. The indications provided by the pathological parameters of the tumour, together with the clinical data related to age, might provide additional information to the histology of sentinel lymph nodes, and might be useful for individualised treatments.

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