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Metastatic potential of small and minimally invasive breast carcinomas

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Abstract Invasive ductal mammary carcinomas (IDC) of 1 cm in tumour size or less account for less than 20% of all IDC. We have observed 167 such cases at our Institution between 1985 and 1989. These were divided into carcinomas with an extensive or predominant intraductal component (EIC or PIC, being least 2× or 4× larger than the invasive component; 90) and compared statistically with the control group (no EIC or PIC; 77) for known prognostic factors and for their metastatic behaviour. Lymph nodes were step sectioned in order to detect occult micrometastases. The median follow up time was 62.6 months. Lymph node metastases were seen in 10% of pT1a and 19% of pT1b cases. Significant differences were found when comparing the EIC/PIC group with the control group (pT1a: 11% vs. 0%, pT1b: 37% vs. 11% lymph node metastases). Also, axillary and infraclavicular recurrence rates were higher for EIC/PIC carcinomas compared with other IDC of ≤ 1 cm (9.3% vs. 4.2%). This significantly adverse metastatic behaviour of the EIC/PIC tumours may be in part due to the more frequent occurrence of multifocal tumours in this group (in 43% vs. 6%), resulting in a greater tumour burden. We conclude that the overall risk of lymph node metastasis is not negligible in carcinomas of 1 cm or less in diameter with the risk being more than doubled for carcinomas with an intraductal component exceeding the invasive tumour by a factor of two. These differences were relevant only to regional metastases; the risk for distant metastasis and survival was identical after 5 years.

Key words Breast cancer · Lymph node metastasis TNM classification · Intraductal component

This work has been dedicated to the 80th birthday of Prof. Drs. h.c. W. Doerr.

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Introduction

Small and minimally invasive breast carcinomas can be divided into two categories: incidental carcinomas with little or no intraductal component and large intraductal carcinomas with microinvasion. Invasive ductal carcinomas (IDC) of less than 1 cm diameter and a small intraductal component are rare and sometimes an unsuspected finding in an otherwise clinically begin appearing breast biopsy. More frequently, small IDC are encountered in conjunction with an extensive or a predominant intraductal component (abbreviated EIC and PIC in this work), because these tumours are as a rule associated with microcalcification and are therefore easily detectable by mammography. The latter association of an IDC with a predominant intraductal component has been considered an entity in the WHO classification of breast carcinomas. The justification for delineating this entity was "that the aggressiveness of ductal carcinomas is to some extent dependant upon the relative amounts of non-invasive and invasive growth" [20]. Further, it was ruled by the WHO that this term should be restricted to cases in which the amount of intraductal carcinoma is at least four times greater than that of the invasive component. In an analogous fashion we have used the term EIC when the intraductal component is at least twice the size of the invasive tumour.

The question if the metastatic potential of small IDC with and without EIC or PIC is similar has important implications for the rational selection of the treatment options that play a role in primary and adjuvant therapy of early breast carcinoma [3, 6, 13, 19]. In order ot analyse this question, we have compared small breast carcinomas with an EIC or PIC with small IDC without this component in a series of consecutively treated mammary carcinomas.

Materials and methods

During the 5 year period from 1985 to 1989, 1,304 patients underwent operative treatment for primary invasive breast carcinoma at the Department of Gynaecology of the University of Heidelberg.

For the purpose of uniformity in classification and the selection of subgroups, all tissue sections of mammary carcinomas from this period were retrieved from the files and re-evaluated by one pathologist. Tumours were classified according to the WHO classification of breast tumours and graded according to the grading system initially proposed by Bloom and Richardson [2].

Out of 938 IDC, 167 cases were small tumours with an invasive component of 1 cm or less (17,8%), i.e. pT1a and pT1b. In cases of multifocal carcinoma, only the size of the largest invasive nodule was considered, in accordance with the TNM system of tumour classification [17]. For example, a carcinoma with an intraductal component of 3 cm and a 0.2 cm microinvasion was classified as pT1a. The size of the invasive component was measured histologically using an occular micrometer and considering the gross description. The size of the non-invasive tumour component was calculated by dividing the number of tissue slices with intraductal carcinoma through the total number of tissue slices minus one and multiplying this with the greatest dimension of the specimen. This indirect, but objective method could be used since as a rule the tumour specimens had been cut perpendicular to the greatest axis and all variables needed for calculation had been recorded.

From these 167 study cases with IDC in the TNM categories pT1a and pT1b the following additional factors were recorded retrospectively: multifocal invasion, vascular invasion, presence of invasive or non-invasive tumour at the resection margins, and the presence of invasive or non-invasive tumour in multiple specimens. The term "multifocality" or "multifocal invasion" was used when one tumour grows in multiple but histologically identical nodules linked by an intraductal or lymphatic component. In contrast, we speak of "multicentricity" only in those rare instances, when independent tumours are present in the same breast. This was not the case in the series presented here. The intraductal component was classified according to its relative size (small, moderate, extensive and predominant, see Table 1), its growth pattern (comedo, solid, cribriform, micropapillary) [11] and its nuclear grade (on a three point scale). We used the term EIC if the non-invasive tumour exceeded the invasive tumour at least twice in diameter and the term PIC if it was at least four times larger than the invasive carcinoma (in accordance with the WHO classification of breast carcinomas [20]). In case of tumours with a PIC, strict criteria were applied for the diagnosis of minimal invasion. Tumour invasion was only considered definitive if invasive cords of tumour cells were identified clearly outside ductal or lobular units and were surrounded by tumour stroma.

The axillary lymph node status was recorded as the number of nodes examined, and in case of lymph node metastases, the number, size, axillary level and pericapsular invasion of the metastases was determined. The lymph node status was available in 157 cases (94%). In order to detect occult micrometastases, the tissue blocks from all cases with minimally invasive carcinomas were retrieved from the files and further step sectioned at 200 µm. These sections were alternatively stained with H&E and monoclonal antibodies against low molecular weight cytokeratins (clones AE1+3, KL1). The immunoreaction weas visualized with the avidin biotin complex method and 3,3-amino-9-ethyl carbazole as substrate. No counterstain was applied.

Table 1 Definitions of the intraductal tumour component in invasive ductal carcinoma (IDC) as used in the text and numer of cases observed in the study period of 1985–1989. The categories "small" and "moderate" ductal carcinoma in situ (DCIS) were not documented separately

Terminology for DCIS component	Relationship DCIS/IDC	All IDC (n=938)	IDC<1 cm (n=167)
None	–	249 (27%)	29 (17%)
Small	DCIS<IDC	507 (54%)	48 (29%)
Moderate	DCIS≥IDC but not >2×		
Extensive (EIC)	DCIS≥2× IDC but not >4×	104 (11%)	18 (11%)
Predominant (PIC)	DCIS≥4× IDC	78 (8%)	72 (43%)

Table 2 Clinical presentation of IDC of 1 m diameter or less comparing tumours with and without an extensive or predominant intraductal component (EIC/PIC)

	IDC with EIC or PIC (*n*=90)	IDC, no EIC or PIC (*n*=77)	*P*-value
Age			
– less or equal 50 years	54 (60%)	28 (36%)	0.0019
– greater than 50 years	36 (40%)	49 (64%)	
Therapy			
– Breast conserving	38 (42%)	54 (70%)	0.0002
– Mastectomy (and subcutaneous mastectomy)	52 (58%)	23 (30%)	
Bilateral mammary carcinoma	7 (8%)	2 (3%)	n.s.
Primary excision not curative	44 (49%)	8 (10%)	<0.0001

During the study period, it was the treatment policy at our Institution to treat breast carcinomas of 3 cm or less by breast conservation therapy (BCT), if there were no surgical or oncological contraindications (such as multicentricity). BCT included the tumour excision with clear margins, axillary lymphadenectomy (axillary levels I, II, sometimes III), and adjuvant whole breast irradiation (50 Gy) using high-dose irradiation with the boost technique as the standard procedure. In the cases presented here, BCT was achievable in 92 cases, while 70 carcinomas were treated with modified mastectomy. In 5 cases (with microinvasive carcinomas) a subcutaneous mastectomy was performed (Table 2). Follow up information was available for all tumours with breast preservation. The median follow-up time was 62.6 months.

Classified values were tested using the two-sided *t*-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. Recurrence rates and crude (observed) survival rates (with death of any causes considered as event) were calculated using the Kaplan-Meier estimator.

Results

Of the 938 IDC, 507 had an intraductal component not exceeding 2× the invasive tumour size (54,1%), and 104 (11,0%) an EIC. An additional 78 (8,3%) tumours were

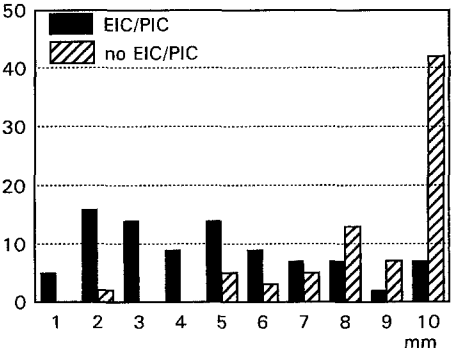

Fig. 1 Size of invasive component in invasive ductal carcinomas with and without an extensive or predominant intraductal component (EIC/PIC)

Table 3 Histopathological characteristics of invasive ductal carcinomas of 1 cm diameter or less comparing tumours with and without an extensive or predominant intraductal component (*n.a.*, not applicable; *n.d.*, not determined; *BCT*, breast conserving therapy)

	IDC with EIC or PIC (n=90)	IDC, no EIC or PIC (n=77)	P-value
Tumour size, invasive component (mm)	4.8±2.6	8.7±1.9	<0.001
Total tumour size (mm) (invasive and non-invasive component)	37.1±20.7	n.d.	n.a.
TNM stage			
– pT 1a	57 (63%)	7 (9%)	<0.0001
– pT 1b	33 (37%)	70 (91%)	
Histological grade			
– 1	16 (18%)	20 (26%)	n.s.
– 2	67 (74%)	46 (60%)	
– 3	7 (8%)	11 (14%)	
Multifocal invasion	39 (43%)	5 (6%)	<0.0001
Vascular invasion	5 (6%)	7 (9%)	n.s.

classified as IDC with a PIC because the ratio between the invasive and non-invasive carcinoma was at least 4× (Table 1).

In the study group of 167 IDC with a maximum tumour diameter of 1 cm (pT1a or 1b), 90 had an EIC a PIC (54%). This is significantly more when compared with the larger IDC (P<0.001). Clinically, patients with EIC and PIC carcinomas (only pT1a and pT1b) differed in a number of aspects from the control group (Table 2). They were significantly younger (P=0.0019), presenting at 49.9±10.8 years of age compared to 56.9±13.7 years. Also, these tumours occured more frequently bilaterally (in 8%). In 58% of EIC and PIC carcinomas the required treatment was mastectomy (because of the larger total tumour size), but only 30% of other IDC with a 1 cm or less invasive component. Also because of the larger tumour size, the primary excision was incomplete in almost 49% of EIC and PIC cases (Table 2).

When comparing the histological results, striking differences in the size distribution of the invasive component are evident (Fig. 1). Statistically, in the group of tumours with an EIC or PIC, the invasive core was singnificantly smaller (averaging 4.8 mm vs. 8.7 mm in the control group). Also most EIC/PIC tumours were in the pT1a category while 91% of the control cases were pT1b. However EIC/PIC carcinomas were six times more often multifocally invasive (Table 3), this was seen in 43% of EIC or PIC carcinomas. No differences were noted with respect to the tumour grade or with vascular invasion (Table 3). The intraductal component was most often of the cribriform type (in 40%) in the EIC/PIC group, while 37% of cases displayed the typical comedo pattern. No statistical differences were seen between pT1a and pT1b tumours concerning the type or grade of the intraductal component.

An average of 18.9 lymph nodes were examined in the study cases, with three routinely cut step sections.

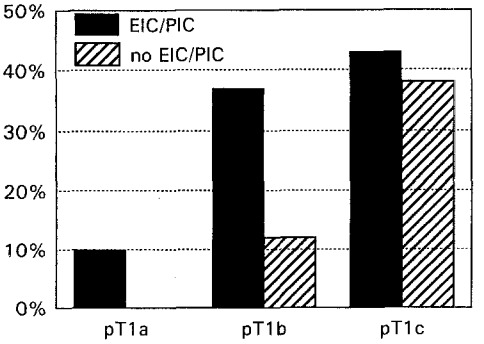

Fig. 2 Relative frequency of lymph node metastases for postoperative T-categories 1a, 1b, and 1c (corresponding to tumour sizes ≤0.5 cm, 0.5–≤1 cm, and 1≤2 cm). Again, invasive ductal carcinomas with and without an EIC or PIC were compared

Table 4 Analysis of axillary lymph nodes in IDC with and without an EIC a PIC component (157 evaluable cases)

	IDC with EIC or PIC (n=84)	IDC, no EIC or PIC (n=73)
Number of axillary nodes examined	19.5±5.1	18.2±5.1
Number of patients with axillary lymph node metastasis in category		
– pT1a (n=53 and 7)	6 (11%)	0
– pT1b (n=31 and 66)	11 (37%)	8 (11%)**
Number of involved nodes per patient		
– 1–3	13 (15%)	6 (8%)
– 4–10	4 (5%)	1 (1%)
> 10	0	0
Pericapsular invasion	6 (7%)	3 (4%)
Highest level of invasion		
– Level 1	15 (18%)	7 (10%)
– Level 2	1 (1%)	0
– Level 3	1 (1%)	0
Maximum diameter		
≤2 mm (micrometastasis)	3 (4%)	2 (3%)
>2 mm (macrometastasis)	14 (17%)	5 (7%)
Average diameter (mm)	6.5±4.9	4.2±3.9
No. of metastases detected only after serial sectioning of lymph nodes	2 (2%)	0

** P=0.05

Significant differences were observed between IDC with and without EIC or PIC. Considering all pT1a and pT1b cases, the EIC/PIC tumours had twice the frequency of axillary lymph node metastases than other IDC. The overall frequency of axillary lymph node metastases in these two groups was 20.2% vs. 9.8% (P=0.05). Differences were seen in all pT1 categories, the lymph node metastasis rates were 11% versus 0% in pT1a, 37% versus 11% in pT1b (P<0.01), and 43% versus 38% in pT1c cases (Fig. 2). Only one IDC without an EIC or PIC had more than three axillary lymph node metastases, while in no instance was the axillary levels two or three involved (Table 4). With further step sectioning of the lymph

nodes an additional two micrometastases only were detected.

Similar differences in metastatic behaviour were noted with respect to ipsilateral axillary and infraclavicular recurrences occurring during follow up. The cumulative 5 year risk for these regional recurrences (excluding intramammary recurrences) was 9.3% in the EIC/PIC group compared with only 4.2% in the control group (calculated using the Kaplan-Meier estimator). This recurrence rate was mainly due to axillary recurrences.

However, no differences were detectable in distant metastases or in the survival analysis. Distant metastases occurred in six evaluable EIC/PIC cases during the follow-up time and five in the control group. The 5 year survival rates were similar with 91.1% in the EIC/PIC group versus 90.2% in the control group.

Discussion

For the purpose of tumour classification only the size of the invasive tumour component is considered for the T category within the TNM system of classification of mammary carcinomas [17]. The justification for this is that for obvious reasons only the invasive component is capable of metastasis and therefore only this component is important for the assessment of prognosis. The assumption is that tumours with a comparable size of invasive component have a comparable capacity for metastasis. However, our data show that IDC have a greater tendency for axillary lymph node metastasis when there is a co-existing EIC or PIC. This relationship could be established for the pT1a and pT1b categories.

It has been amply documented that the presence of an EIC is an adverse factor for local control of mammary carcinoma [1, 4, 5, 7, 10, 14, 16]. This is mostly due to the presence of residual tumour after breast conserving therapy, but is also related to the association of EIC carcinomas with other adverse prognostic factors, such as young age [8, 12] and multiple synchronous cancers [9]. These factors must be taken into account when considering possible reasons to explain this difference in metastatic potential between IDC with and without EIC or PIC. It is probable that EIC and PIC cases have a larger overall invasive tumour mass than is indicated by the pT category because of their tendency for multifocal tumour invasion. Although in our study the mean size of the largest invasive nodule was only 4.8 mm compared with 8.7 mm in other IDC of less than 1 cm, the EIC/PIC group had evidence of multifocal tumour invasion in 43% of the cases. Since EIC/PIC carcinomas can reach several centimetres in size, this fact alone may contribute largely for the differences in metastatic potential. Another factor that should be considered here is the patient age. EIC/PIC patients were significantly younger than the control group, approximately 60% being 50 years of age or younger. Youth is often correlated with more aggressive behaviour of breast cancer and an increased tendency for metastasis formation [8, 12, 15].

For practical purposes, it may be concluded that strict definitions as to what exactly constitutes an EIC or PIC are helpful in defining subgroups of different biological behaviour. Unfortunately, these terms have been used with different connotations, and this may have contributed to the varying percentages of EIC in the literature [18]. We recommend that the absolute size of the intraductal and of the invasive tumour components should be determined, and that appropriate terms should be used to describe the relationship of both components. The method of indirect determination of these measurements that is described here has been used recently at our Institution without problems.

This analysis of the metastatic potential of small and microinvasive breast cancers allows us to draw the following conclusions: the risk of local and locoregional metastatic spread is not negligible in carcinomas of 1 cm or less in size; there are differences when comparing carcinomas with and without an EIC a PIC, with the risk for axillary metastases being approximately twice for the first group, and that these differences are relevant only to regional metastases; the risk for distant metastasis and survival was identical.

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