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Original article

Correlation of size and focality with prognosis in small breast carcinoma: a single institution case series

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ABSTRACT

Aim of the study: The clinical behavior and prognosis of small multifocal and microinvasive breast cancers are still debated together with the best method of assessing tumor size in multiple invasive carcinomas. This study evaluates the clinico-pathological features of single and multiple breast cancers up to 0.5 cm in order to evaluate the rate of recurrences.
Materials and methods: We retrospectively analyzed 170 node-negative patients consecutively treated at European Institute of Oncology from 2001 to 2006. We divided them into Group I (pT1mi) and Group II (pT1a) furtherly divided in subgroups, according to focality and aggregate diameter. For each group we assessed tumor size, (multi)focality, extensive in situ component (EIC), histology, grade, peritumoral vascular invasion (PVI), hormonal receptor status (HR), HER-2 expression, Ki67 expression.
Results: We observed that the frequency of local recurrences and distant metastases in group I was higher among those with a single focus; whereas in group II, it was higher in multifocal carcinomas. Then, by comparing the two groups, the prognosis was better in multiple pT1mi than in similarly sized unifocal pT1a.
Conclusions: Microinvasive carcinomas are associated with a good prognosis, even if they seem to have a more aggressive intrinsic biological behavior. Multifocality seems to be correlated with a worse prognosis in case of invasive carcinomas pT1a. In case of microinvasive carcinomas, by contrast, multifocality *per se* does not seem to affect the recurrence rate.
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Moreover, aggregate diameter is not correlated with an increased risk of recurrences and should not be used for staging.

1. Introduction

Tumor size and axillary lymph node status are two of the most important prognostic factors in breast cancer. Methods for tumor size measurement are not internationally standardized especially in the setting of multiple (multifocal/multicentric) microinvasive tumors.

Microinvasive carcinoma is a rare entity and accounts for 0.7–2.4% of all breast cancers [1]. It is almost always encountered in association with ductal carcinoma in situ (DCIS) (Fig. 1) and rarely in the absence of carcinoma in situ.

The term "microinvasive" carcinoma was first introduced in 1982 to indicate an invasive focus measuring 1 mm or less [2]. Afterwards, many other definitions have been proposed [3]. Currently, the AJCC staging manual defines microinvasive carcinoma as "invasive carcinoma with no focus measured larger than 1 mm" and still includes microinvasive carcinoma in the T staging system, categorized as pT1mi [4].

Furthermore, in the TNM staging manuals, another issue has been addressed: when multiple tumor foci are present, the number of foci should be determined and the largest diameter of the largest tumor focus should be reported for pTNM staging [4].

Multiple invasive carcinoma is defined as the presence of two or

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Abbreviations

DCIS	ductal carcinoma in situ
AJCC	American Joint Committee on Cancer
CAP	College of Pathologists
OS	overall survival
DFS	disease free survival
EIC	extensive in situ component
ER	estrogen receptor
PgR	progesterone receptor
WHO	World Health Organization

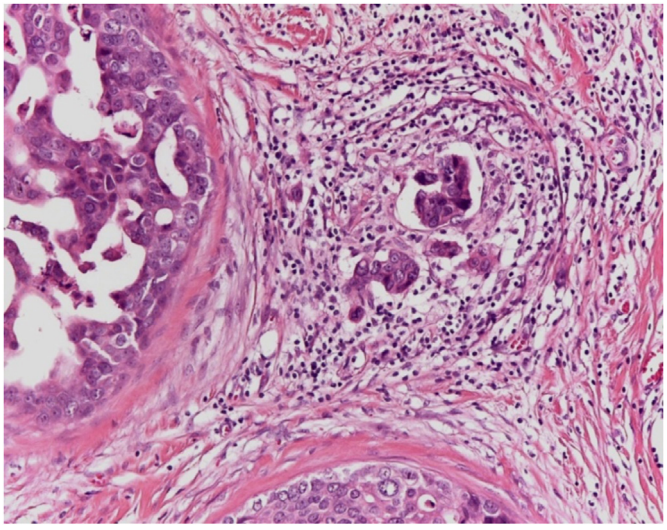

Fig. 1. An invasive focus of breast carcinoma cells up to 1 mm in largest diameter, between two ducts with solid DCIS and surrounded by lots of lymphocytes (Hematoxylin and Eosin stain; original magnification 400x).

more invasive tumor foci separated from each other by normal breast tissue [5] and it could be associated with a worse prognosis in terms of axillary lymph node involvement and survival rate [6,7].

When considering tumors with multiple foci not macroscopically separated and appearing as a unique mass lesion, lack of standardized methods of measurement may cause difficulties in assessing T stage, and pathologists may adopt different criteria for staging these tumors.

According to the last American College of Pathologists (CAP) guidelines, if multiple carcinomas are present, the size of the largest invasive focus is used for T classification with "m" modifier between brackets, indicating multiple foci. In case of multiple invasive carcinomas in close proximity, it may be difficult to distinguish multiple adjacent foci from one large invasive carcinoma during gross examination [4]. So, careful inspection of the specimen with submission of intervening tissue between grossly identified tumor foci is recommended.

While this staging procedure is easily applicable to larger tumor foci, it may be more difficult to adopt in case of multiple small or microinvasive carcinomas. Indeed, another method to define the T stage for the latter tumors is based on the macroscopically assessed diameter of the lesions identified during sampling, including both in situ and invasive foci, considered as a unique mass lesion [8]. This measurement method may be important to avoid underestimation of the actual size of multiple tumors, leading to a possible higher risk of local recurrence and axillary lymph node metastases [9]. Moreover, the precise evaluation of tumor size is of paramount importance as it still influences clinical decisions, even if biological and molecular characteristics drive the final decision offering a tailored therapy [10].

Given the differences between the microscopic and macroscopic measurement methods and the prognostic value of tumor size, the aim of this study was to analyze clinical outcomes of microinvasive carcinoma pT1mi (single and multifocal) and small invasive carcinoma pT1a (single and multifocal), comparing them in terms of overall survival (OS) and disease free survival (DFS).

2. Material and methods

Searching the file of the Pathology Department of the European Institute of Oncology from 2001 to 2006, we identified 1312 cases of node-negative invasive breast cancers with extensive (>25%) in situ component (EIC) [11]. Then, we selected 170 consecutive patients with node-negative invasive breast cancer, single and multifocal, ranging from microinvasive (pT1mi) up to 0,5 cm (pT1a) that were consecutively treated at our Hospital and satisfied the following inclusion criteria.

Patients with positive personal medical history for breast cancer, cases of invasive tumor focus larger than 0,5 cm and patients whose breast cancer was diagnosed on pre-operative biopsy were excluded from the study. Samples showing the presence of invasive carcinoma on resection margins were not included in the study.

All patients underwent total mastectomy or breast-conserving surgery followed by radiation therapy, sentinel lymph node biopsy or axillary lymph node dissection. The surgically obtained breast tissue specimens were sampled for histology following institutional guidelines.

In the absence of a macroscopically identifiable mass lesion, complete submission of the entire suspicious area was required. The specimen was sliced at approximately 4–5 mm intervals, and consecutive blocks of the whole abnormal area (including adjacent fibrotic tissue and microcalcifications) was submitted to detect any possible microinvasive focus.

From each paraffin-embedded block, 3–5 μm tick sections were cut and stained with hematoxylin and eosin and further histological sections were taken for ancillary studies.

Each case was examined by one or more pathologists who assessed the pathologic characteristics including tumor size, multifocality, EIC, histology, grade, peritumoral vascular invasion, estrogen (ER) and progesterone receptor (PgR) status, HER-2 expression and Ki67 expression.

Multifocality and EIC were defined according to CAP guidelines [11].

Tumor grade and tumor type were assessed in accordance, respectively, with the Nottingham Grading System [12] and WHO [13]. In order to get more reproducible results, cases have been blindly revised by two pathologists and in case of disagreement, a third experienced pathologist's opinion was required.

The expression of ER and PgR and the tumor proliferative fraction were evaluated immunohistochemically as previously reported [14].

HER-2 overexpression was also investigated immunohistochemically, using a specific polyclonal antiserum (Dako® Glostrup, Denmark, working dilution 0.05 mol/L), according to the manufacturer's instructions.

For the purpose of the current analysis, we re-evaluated all the H&E-stained slides of the 170 tumors, recording the number and size of all invasive foci, and calculating the aggregate diameter of all foci in case of multifocal tumors.

Cases of our study were then divided into two main groups

according to their sizes: (Group I) microinvasive carcinomas (pT1mi) and (Group II) invasive carcinomas (pT1a). Each group was further divided into 3 subgroups according to focality and aggregate diameter: (Group IA) single focus up to 0,1 cm, (Group IB) multiple foci up to 0,1 cm and (Group IC) multiple foci with an aggregate diameter ranging from 0,1 to 0,5 cm; (Group IIA) single focus up to 0,5 cm, (Group IIB) multiple foci up to 0,5 cm and (Group IIC) multiple foci with an aggregate diameter ranging from 0,5 cm–1 cm.

3. Results

On the basis of these inclusion and exclusion criteria, 170 cases of breast cancer were divided into 70 cases classified as microinvasive carcinoma (I, pT1mi), either unifocal or multifocal, and 100 cases classified as invasive carcinoma (II, pT1a).

The median follow-up was 108 months for patients with diagnosis of microinvasive carcinoma and 123 months for patients with diagnosis of pT1a invasive carcinoma.

Of the 70 microinvasive carcinomas, 41 were unifocal (IA), and 29 were multifocal (IB,C). Eleven of the latter tumors displayed multiple foci with an aggregate diameter less than 0,1 cm (IB) and 18 had an aggregate diameter more than 0,1 cm but less than 0,5 cm (IC).

Among the 29 (IB,C) cases of multiple microinvasive carcinomas, 13 of them (45%) had been reported as mass lesion more than 2 cm identified by gross examination.

Tables 1 and 2 show the clinico-pathological characteristics of the 70 (I) patients with microinvasive carcinomas. We observed no significant difference in terms of mean age of diagnosis for patients with unifocal (IA) microinvasive carcinomas (54 years) and patients with multiple carcinomas (IB,C) (53 years (IB) *vs* 50 (IC) years). The most frequent histological type was the same, both in unifocal and in multiple microinvasive carcinomas: invasive carcinoma of no special type (invasive ductal carcinoma) (94%, 66/70). Tumors were grade 1 in 12% of these cases (n = 8), grade 2 in 44% (n = 31) and grade 3 in 44% (n = 31). Of the 70 microinvasive carcinomas, 73% (51/70) had a median Ki67 labelling index ≥14% and 20% (14/70) <14%.

Of the 41 unifocal microinvasive carcinoma (IA), 39% were hormone receptor (HR)-positive; among the 11 multiple microinvasive carcinoma with aggregate diameter less than 0,1 cm (IB), 18% were HR-positive; finally, among the 18 multiple microinvasive carcinoma with aggregate diameter less than 0,5 cm (IC), 50% were HR-positive.

Microinvasive carcinomas (I) were associated with a local recurrence in 5 cases (7.1%) and, among them, 4 (80%) had single microinvasive focus. There were no distant metastases reported for these patients.

pT1a invasive carcinoma was diagnosed in 100 cases: 52 of them were unifocal carcinoma (IIA), the remaining 48 were multifocal (IIB,C). Of the latter, 32 were multiple carcinomas with an aggregate diameter less than 0,5 cm (IIB) and 16 an aggregate diameter more than 0,5 cm but less than 1 cm (IIC).

Among the 48 (IIB,C) cases of multiple invasive carcinomas pT1a, 30 of them (62,5%) had been reported as mass lesion of more than 2 cm identified by gross examination.

Tables 3 and 4 show the clinico-pathological characteristics of the 100 patients with invasive carcinomas pT1a. We observed no significant difference in terms of mean age at diagnosis of the patients with unifocal (IIA) (52 years) or multifocal (IIB,C) carcinomas (53 years (IIB) and 50 years (IIC). The most frequent histological type was the same both (II) in unifocal and in multiple carcinomas: invasive carcinoma of no special type (invasive ductal carcinoma) (91%, 91/100). Tumors were grade 1 in 24% of these cases (n = 23), grade 2 in 46% (n = 44) and Grade 3 in 30% (n = 29). Fifty-six tumors had a Ki67 labelling index >14% and 43 ≤ 14%.

Of the 52 (IIA) patients with pT1a unifocal invasive carcinoma, 83% had HR-positive tumors; among the 32 multiple invasive carcinomas with aggregate diameter less than 0,5 cm (IIB), 59% were HR-positive; finally, among the 16 multiple invasive carcinomas with aggregate diameter less than 1 cm (IIC), 62% were HR-positive.

Table 1
Microinvasive (single/multifocal) clinico-pathological characteristics.

	Single focus (Ia) pT1mi (n = 41 patients)	Multiple foci (Ib) pT1mi AD[a] ≤ 1 mm (n = 11 patients)	Multiple foci (Ic) pT1mi 1 mm < AD[a] ≤ 5 mm (n = 18 patients)
Mean age (ys)	54	53	50
Histotype		11/11 (100%)	18/18 (100%)
NST (ductal)	37/41 (90%)	–	–
Lobular	1	–	–
Mucinous	1	–	–
Micropapillary	1	–	
Apocrine	1		–
Grade		–	–
G1	8/41 (19.5%)	2/11 (18%)	11/18 (61%)
G2	18/41 (44%)	9/11 (82%)	7/18 (39%)
G3	15/41 (36.5%)		
HR[a] status		2/11 (18%)	9/18 (50%)
ER+	16/41 (39%)	1/11 (9%)	6/18 (33%)
PGR+	9/41 (22%)		
Proliferation rate		–	3/18 (17%)
Ki67 ≤ 14%	11/41 (27%)	10/11 (91%)	15/18 (83%)
Ki67 > 14%	26/41 (63%)	1/11 (9%)	
Ki67 NA[a]	4/41 (10%)		
HER2/neu (IHC 3+)	16/41 (39%)	7/11 (63%)	10/18 (55%)
Peritumoral vascular invasion	2/41 (5%)		
Size lesion by gross examination		–	2/18
0.1–1 cm	5/41 (1 REC[a])	5/11	2/18 (1 REC[a])
1.1–2 cm	7/41	1/11	6/18
2.1–5 cm	10/41 (2 REC[a])	4/11	2/18
>5 cm	7/41 (1 REC[a])	1/11	6/18
NA	12/41		

[a] AD: aggregate diameter; HR: hormonal receptor; NA: not available; REC: ipsilateral recurrence.

Table 2
Morphological and biological features of recurrent pT1mi (single or multifocal) tumors.

n	Microscopic invasive size (mm)	Macroscopic size (cm)	ER[a] %	PgR[a] %	Her2%	Ki67%	Tx[a]	TR[a]	DFS[a] (mo)
1	0.4 (single)	5.3	0	0	3+ (90%)	10	RT[a]	DCIS[a]	50
2	1 (single)	3.5	90	2	0	10	RT + HT[a]	DCIS[a]	52
3	1 (single)[b]	2.5	0	0	3+(95%)	20	RT[a]	DCIS[a]	84
4	0.5 (single)	0.9	0	0	2(50%)	12	RT[a]	IDC[a]	36
5	1 (multifocal)	1.5	40	15	0	20	RT[a]	DCIS[a]	25

[a] ER: estrogen receptors; PgR: progesterone receptors; Tx: Therapy; TR: Type of recurrence; DFS: Disease free Survival; RT: Radiotherapy; HT: Hormonal Therapy; DCIS: Ductal Carcinoma in Situ; IDC: Invasive Ductal Carcinoma.
[b] Distant margins <1 mm.

Table 3
(Macro)Invasive (single/multifocal) clinico-pathological characteristics.

	Single focus (IIa) pT1a (n = 52 patients)	Multiple foci (IIb) pT1a 1 mm < AD[a] ≤ 5 mm (n = 32 patients)	Multiple foci (IIc) pT1a 5 mm < AD[a] ≤ 10 mm (n = 16 patients)
Mean age (ys)	52	53	50
Histotype		30/32 (94%)	14/16 (88%)
NST (ductal)	47/52 (90%)	1/32 (3%)	1/16 (6%)
Lobular	2/52 (4%)	–	1/16 (6%)
Mucinous	3/52 (6%)	–	–
Micropapillary	-	1/32 (3%)	–
Apocrine	-		
Grade		8/32 (25%)	1/15 (7%)
G1	14/49 (28.5%)	14/32 (44%)	8/15 (53%)
G2	22/49 (45%)	10/32 (31%)	6/15 (40%)
G3	13/49 (26.5%)		
HR[a] status		19/32 (59%)	10/16 (62%)
ER+	43/52 (83%)	14/32 (44%)	9/16 (38%)
PgR+	33/52 (62%)		
Proliferation rate		11/32 (34%)	3/16 (19%)
Ki67 ≤ 14%	29/52 (56%)	20/32 (63%)	13/16 (81%)
Ki67 > 14%	23/52 (44%)	1/32 (3%)	–
Ki67 NA[a]	-		
HER2/neu (IHC 3+)	14/52 (27%)	15/32 (47%)	10/16 (62%)
Peritumoral vascular invasion	1/52 (2%)	3/32 (9%)	
Size lesion by gross examination		2/32	–
0.1–1 cm	6/52	9/32 (2 REC[a])	3/16 (1 MET[a])
1.1–2 cm	11/52 (1 REC[a]/1 MET[a])	13/32 (2 REC[a]/1 MET[a])	8/16 (1 REC[a])
2.1–5 cm	14/52 (1 REC/1 MET[a])	5/32	4/16
>5 cm	7/52	3/32	1/16
NA	14/52 (1 REC[a])		

[a] AD: aggregate diameter; HR: hormonal status; NA: not available; REC: ipsilateral recurrence; MET: Metastasis.

Table 4
Morphological and biological features of recurrent pT1mi (single or multifocal) tumors.

n	Microscopic invasive size (mm)	Macroscopic size (cm)	ER[a] %	PgR[a] %	Her2 %	Ki67%	Tx[a]	TR[a]	DFS[a] (mo)
1	1.9 (single)	3	80	0	3+ (20%)	41	RT[a] + HT[a] (HT noncompliant)	IDC[a]	50
2	3 (single)	1.8	0	0	1+	10	None (pregnant)	DCIS[a]	9
								IDC[a]	73
3	2.5 (single)	1.7	95	0	0	5	RT + HT[a]	Distant Metastases	51
								Death	192
4	4.5 (single)	2.8	90	5	0	18	RT + HT[a]	Distant Metastases	61
5	2 (single)	NA	95	95	1	10	RT + HT[a]	IDC[a]	120
6	2.8 (multifocal)	2.4	90	0	3+ (90%)	18	RT + HT[a] (RT noncompliant)	IDC[a]	30
7	2.5 (multifocal)[b]	2.3	60	70	0	8	RT + HT	ILC[a]	74
8	2.6 (multifocal)	5	0	0	3+ (95%)	33	None	Distant Metastases	63
								Death	76
9	4 (multifocal)	1.3	60	2	3+ (40%)	10	RT + HT[a] (HT noncompliant)	DCIS[a]	21
								IDC[a]	60
10	2.6 (multifocal)[b]	1.5	0	0	3+ (90%)	25	RT[a]	DCIS[a]	19
11	7 (multifocal)	1.4	90	90	0	12	RT + HT[a]	Distant Metastases	98
								Death	120
12	7.7 (multifocal)	3	0	0	3+ (90%)	24	None	IDC[a]	36

[a] ER: estrogen receptors; PgR: progesterone receptors; Tx: Therapy; TR: Type of recurrence; DFS: Disease free Survival; RT: Radiotherapy; HT: Hormonal Therapy; DCIS: Ductal Carcinoma in Situ; IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma.
[b] Distant margins <1 mm.

Among these 100 patients, 12 (12%) experienced local recurrences and/or distant metastases.

In detail, 5 (9.6%) of 52 patients with single pT1a carcinoma (IIA) experienced recurrences, including 2 (3.8%) patients with axillary lymph node and distant metastases. Of 32 patients with multiple invasive carcinomas with aggregate diameter less than 0,5 cm (IIB), 5 (15.6%) developed recurrences, including 1 (3.1%) with distant metastases. Of the 16 patients with multiple invasive carcinoma with aggregate diameter more than 0,5 but less than 1 cm (IIC), 2 (12.5%) developed recurrences, including 1 (6.25%) distant metastases.

4. Discussion

One of the most important prognostic factors in breast carcinoma is tumor size. In unifocal breast carcinomas, the largest diameter of the tumor is reported for TNM staging while in multiple tumors, according to recent guidelines and staging systems, satellite foci should not be taken into account and largest tumor focus should be used for staging [4].

In this study we retrospectively examined 170 cases of breast carcinoma including microinvasive (pT1mi) and invasive carcinomas (pT1a), both unifocal and multifocal, to compare clinical outcomes between groups and subgroups.

Many studies have reported that the risk of lymph node involvement and metastatic dissemination increases as the tumor size increases and, moreover, several studies revealed a worse prognosis in multiple carcinomas [15,16]. Additionally, it is well known that the presence of extensive intraductal component correlates with a higher risk of recurrences mostly in cases of small/microinvasive carcinoma [11].

In our study, we confirmed that the frequency of local recurrence and distant metastases is related to the T staging category: in microinvasive carcinomas it is lower than in pT1a carcinomas; indeed, patients with microinvasive carcinoma experienced only 5 cases (7.1%) of recurrence in contrast to patients with pT1a invasive carcinoma presenting with 12 cases (12%) of recurrence, including 4 distant metastases.

These results confirm that the greater the size, the greater the risk of breast recurrence and metastases.

However, when considering subgroups, more specifically patients with unifocal (IA) microinvasive breast cancer *vs* patients with unifocal (IIA) invasive breast cancer pT1a, we observed that the percentage of local recurrence was comparable, respectively 9.7% (4/41) in the pT1mi group and 9.6% (5/52) in the pT1a group. This may suggest a more aggressive intrinsic biological behavior of microinvasive carcinoma as other studies propose [17]. This is furtherly supported by observing that microinvasive carcinomas show different HR-status, HER-2 overexpression and proliferation rate, when compared with invasive carcinomas pT1a.

Indeed, by analyzing hormone receptor status, we observed that only 38.5% of (IA) microinvasive carcinomas were HR-positive, in contrast with invasive (IIA) carcinoma where 72% were HR-positive.

In accordance with other studies [18–20], we observed that HER-2 overexpression was more commonly detected in microinvasive (IA) carcinomas compared with invasive (IIA) carcinomas pT1a (47% of the microinvasive carcinomas pT1mi *vs* 39% of the pT1a invasive carcinomas).

When comparing patients with unifocal (IIA) invasive breast cancer pT1a vs patients with similarly sized multifocal (IIB) invasive breast cancer pT1a(m), we observed that the percentage of recurrences was higher in the latter group (5/52 9.6% vs 5/32 15.6%).

Thus, multiple carcinomas appear to be associated with a worse prognosis as other studies suggest [6,15,16]. However, this was not confirmed when considering multiple microinvasive carcinomas. Indeed, by comparing patients with unifocal (IA) microinvasive carcinomas pTmi vs patients with similarly sized multiple (IB) microinvasive carcinomas pT1mi(m) we found out that the number of recurrences was higher in the former group (4/41 9.75% vs 0/11 0%).

This may suggest that in case of microinvasive carcinomas, multifocality does not affect the prognosis.

The more interesting question we wanted to address, however, was whether the aggregate diameter of the multifocal tumors had a greater prognostic value.

To answer this question, we compared two subgroups: patients with multiple microinvasive carcinomas with an aggregate diameter more than 0.1 cm but less than 0.5 cm (IC) and patients with similarly sized unifocal carcinomas (IIA). We observed that the number of recurrences was lower in the former than in the latter (5.5% vs 9.6%), confirming that multifocality does not correlate with the risk of breast recurrence in case of microinvasive carcinomas and calling into question the accuracy of the aggregate diameter in determining the T stage and as a consequence, the prognosis.

The implications of the results of this study for the management of patients with small invasive breast cancer, either unifocal or multifocal, are manifold:

i) the value of an accurate histopathological assessment of the actual size of the invasive component in tumors with extensive or predominant in situ component cannot be overemphasized. Indeed, most of the tumors of the current series presented as a mass lesion, with a T2 or T3 clinical stage. In such cases, the accurate pathological staging of the invasive component is of paramount importance to inform the choice of the adjuvant systemic treatment. The goal is easily achievable in case of unifocal invasive tumors, but much more complex for multifocal tumors;

ii) the need for an extensive search for any microinvasive focus in an otherwise DCIS is also re-emphasized. Indeed, even the identification of a single microinvasive focus correlates with a 10% risk of a breast cancer event during the follow-up;

iii) a thorough evaluation of the histological size of the invasive foci (1 mm or less vs > 1–5 mm) is strongly recommended, because size correlates with a different rate of recurrence (7.1% vs 12%);

iv) multifocality *per se* does not seem to affect the recurrence rate for microinvasive tumors;

v) summing up the size of multifocal microinvasive foci and using the aggregate diameter to stage the tumors is not justified. Indeed, by comparing patients with unifocal pT1a carcinoma and patients with similarly sized multiple (IC) carcinomas pT1mi(m), the recurrence rate was higher in the first group. In accordance with the AJCC, these results strongly confirm that in case of multiple carcinomas, the largest diameter of the largest tumor focus should be reported for TNM staging without summing up the size of satellite foci.

A strength of the current study is its mono-institutional nature (thus ensuring a homogeneous diagnostic approach and treatment during the study period) and the longer follow-up time (median 108 months) then many other reports [21–23] allowing detection of late recurrences.

On the other side, major limitations are its retrospective nature, and the relatively small number of patients in the different cohorts, precluding the possibility to perform multivariable analysis.

5. Conclusions

In conclusion, we emphasize the role of the accurate histopathological assessment of tumor size in case on small invasive tumors associated with an extensive or predominant in situ component, to avoid as much as possible any under- or over-treatment of the patients.

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Author contributions

Mauro G. Mastropasqua and Sara Pirola: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft. Francesca Addante: Data curation, writing. Giuseppe Ingravallo: Software. Giuseppe Viale: Supervision, reviewing and editing.

Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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