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Original Article

Impact of the presence and quantity of ductal carcinoma in situ component on the outcome of invasive breast cancer

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Abstract: Introduction: The role of ductal carcinoma in situ (DCIS) component on the outcome of invasive breast cancer is not yet completely clear. Our study aims to assess the impact of the presence and quantity of DCIS component on the outcome of patients operated for invasive breast cancer. Materials and methods: We collected retrospective data about patients operated at their breast for invasive cancer between 2007 and 2012, focusing on the presence of DCIS component. Then, we divided patients into four groups based on the quantity of DCIS component as follows: not found (group A), minimal (group B, <25%), extensive (group C, 25-75%), and prevalent (group D, >75%). We further defined "extensive intraductal component" (EIC) groups C and D together. Results: DCIS component was associated with young age, familial history of breast cancer and worse biological characteristics, including high grading, higher prevalence of Her2/Neu overexpression, hormone receptors negativity, comedo-like necrosis and multifocality/multicentricity. Despite the unfavorable prognostic factors, invasive cancers associated with EIC were frequently treated with radical surgery and resulted to have long disease-free survival and low local recurrence rate. In patients with DCIS component (groups B, C, and D) the extension of this component resulted indirectly correlated with local recurrence rate, tumor lymphovascular invasion, and lymphnode extracapsular invasion. The highest prevalence of local recurrences was found in group B, which tended to be less frequently treated with radical surgery than group D (P<0.05) and C (P=n.s.). Conclusions: Different clinical and tumor features among invasive breast cancer with and without DCIS component indicate that they are distinct entities probably originating by different pathways that deserve to be studied. Furthermore, the controversial results about the management of cancer with minimal intraductal component require further studies in order to reduce local recurrence.

Keywords: Breast cancer, ductal carcinoma in situ component, extensive intraductal component, overall survival, disease-free survival

Introduction

Ductal carcinoma in situ (DCIS) is found in a great number of pathological specimens to accompany invasive breast cancer, being sometimes very limited, while representing some other times the majority of the neoplastic lesion. Owing to this correlation and other evidences present in the literature DCIS is considered as a non-obligate precursor of invasive breast carcinoma [1]. However, in the literature are recorded also cases of invasive breast cancer without coexistence of DCIS especially among triple negative cancers [1]. Anyway, the co-existence of a DCIS component with the invasive breast cancer has always been described as a marginal aspect of invasive breast cancer, until Schnitt and colleagues introduced the definition of "extensive intraductal component" (EIC) as the presence of 25% or more intraductal neoplasia in an invasive breast carcinoma [2], and the group of Veronesi took EIC into consideration in their new breast cancer classification [3].

An abnormal mammographic finding is by far the most common presentation of DCIS, which in the most cases appears as a cluster of microcalcifications [4, 5]. As a consequence, after the introduction of an organized breast cancer screening by mammography in our region, we observed a remarkable increase in the detection rate of pure DCIS (23% of non palpable breast lesions) and an increased incidence of EIC [6-9]. This increase may be explained by the greater attention that pathologists payed in intraductal component search and description. However, an alternative explanation could also be the high sensitivity of mammography for intraductal neoplasia that helps in detecting very small invasive breast cancer associated with EIC.

The role of EIC on breast cancer prognosis remains unclear, and its surgical management is still argument of debate. In fact, the presence of DCIS remains one of the principal risk factors for breast demolition, due to its usual multifocality and multicentricity [10-13], and its frequent correlation with margin infiltration in case of breast conservative surgery (BCS) [14, 15], so that there is still disagreement when considering what constitutes an adequate margin of excision in DCIS. In addiction, EIC has been demonstrated to be an independent risk factor for local recurrence after BCS especially in young, premenopausal women [16, 17], and for residual disease in completion mastectomies after BCS [18]. Moreover, the incidence of nipple involvement in DCIS has become always more relevant with the increasing interest in nipple-sparing mastectomies [19].

Although DCIS is well recognized to be a possible precursor of invasive ductal carcinoma [20, 21], the proportion of women with mammographically detected DCIS in whom invasive carcinoma will develop within their lifetimes is uncertain, as well as the proportion of biologically indolent DCIS which is unlikely to become clinically significant. And the literature is lacking about the role of intraductal component by the presence of an invasive breast cancer. Then, our study aims to assess the impact of the presence and quantity of intraductal component on the outcome of patients operated for invasive breast cancer.

Materials and methods

We retrospectively analyzed data form our registry about all women operated at their breast for invasive breast cancer in our Clinic between January 2007 and December 2012. This retrospective chart review study was designed according to the Declaration of Helsinki and it was approved by the Internal Review Board (IRB). Moreover, this study regarding consent for processing data used in this retrospective analysis follows the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority (Authorization no. 9/2013). In the present study we included only cases of invasive breast cancer where the DCIS component extension was mentioned. The study population was divided into four groups in accordance with DCIS component quantity, as follows: group A) DCIS not found in standard slides; group B) minimal DCIS extension (<25% of the neoplastic lesion), group C) extensive (25-75%), and group D) prevalent (>75%). We further defined "extensive intraductal component" (EIC) groups C and D together. Pathological specimens were routinely assessed as suggested by the European guidelines [22]. Samples approximately 30 mm or less in maximum diameter were completely sliced, embedded and examined histologically while for larger specimens sampling was done according to the European guidelines [22].

Clinical and histological information

Collected data included the following clinical and pathological factors. Patient characteristics: age at diagnosis, body mass index (BMI), familial history of breast cancer, fertility status, and eventual use of therapies containing estrogens. Tumor characteristics were considered as follows: histological type, TNM classification (VII ed. AJCC/UICC, 2009), tumor grading, Mib1/Ki-67 proliferation index, hormone receptors status including estrogen receptor (ER), progesteron receptor (PR) and HER2/neu expression, and other microscopic features evaluated in the new classification proposed by the group of Veronesi such as multifocality/multicentricity, peritumoral vascular invasion (PVI), peritumoral inflammation, lymph node extracapsular invasion or bunched axillary lymph nodes [3].

Tumor histology was classified according to the World Health Organization criteria [23, 24] and tumor grade was evaluated following the recommendations of Elston and Ellis [25]. Multifocality/multicentricity, PVI, peritumoral inflam-

Table 1. Characteristics of the population subdivided by intraductal component extension

	Not found (A)	Minimal (B)	Extended (C)	Prevalent (D)	
Age (years)	59.81 (±12.51)	58.42 (±12.07)	56.9 (±12.01)	58.04 (±12.22)	(2)
Age <50 years	23.6% (137/580)	28.4% (56/197)	31.4% (60/191)	31.1% (14/45)	(2)
BMI (kg/m^2)	25.88 (±5.25)	25.96 (±5.47)	25.89 (±4.77)	25.46 (±4.77)	ns
Tobacco smoke	4.3% (21/487)	8.6% (12/139)	6.2% (10/160)	2.6% (1/39)	(1)
Familial history of breast cancer	35.6% (64/180)	32.6% (30/92)	53.8% (35/65)	53.8% (7/13)	(2, 4)
Use of OC	39.5% (32/81)	46.4% (13/28)	48.5% (16/33)	0% (0/9)	(3, 5, 6)
Post-menopausal status	81.2% (471/580)	76.6% (151/197)	69.6% (133/191)	73.3% (33/45)	(2)
First breast surgical treatment					
BCS	63.4% (368/580)	62.4% (123/197)	52.9% (101/191)	44.4% (20/45)	(2, 3, 5)
Mastectomy	36.6% (212/580)	37.6% (74/197)	47.1% (90/191)	55.6% (25/45)	(2, 3, 5)
Axilla surgical treatment					
CALND	41.9% (243/580)	46.7% (92/197)	43.5% (83/191)	31.1% (14/45)	ns
SLNB	55.2% (320/580)	51.3% (101/197)	55.5% (106/191)	64.4% (29/45)	ns
None	2.9% (17/580)	2% (4/197)	1% (2/191)	4.4% (2/45)	ns
Second breast surgical treatment					
Nothing	82.1% (302/368)	78.9% (97/123)	61.4% (62/101)	50% (10/20)	(2, 3, 4, 5)
BCS	8.2% (30/368)	9.8% (12/123)	16.8% (17/101)	15% (3/20)	(2)
Mastectomy	9.8% (36/368)	11.4% (14/123)	21.8% (22/101)	35% (7/20)	(2, 3, 4, 5)
Mastectomy as definitive treatment	42.8% (248/580)	44.7% (88/197)	58.6% (112/191)	71.1% (32/45)	(2, 3, 4, 5)
Other treatments					
Neoadjuvant	5.5% (32/580)	2% (4/197)	3.1% (6/191)	6.7% (3/45)	(1)
Adjuvant radiotherapy	61.1% (350/573)	60.2% (118/196)	50.5% (94/186)	27.3% (12/44)	(2, 3, 5)
Adjuvant chemotherapy	39.3% (225/573)	47.4% (93/196)	47.3% (88/186)	18.2% (8/44)	(1, 3, 5)
Adjuvant hormonaltherapy	79.2% (454/573)	81.6% (160/196)	82.8% (154/186)	54.5% (24/44)	(3, 5)

Significant differences between: 1) Absent vs. Minimal; 2) Absent vs. Extended; 3) Absent vs. Prevalent; 4) Minimal vs. Extended; 5) Minimal vs. Prevalent; 6) Extended vs. Prevalent. (ns) = non significant.

mation, lymph node status was defined as previously described [26, 27]. The expression of ER, PR, and Her-2/Neu were evaluated by immunohistochemistry. We considered ER or PR receptor positivity as positive in any nuclear staining ≥1%. We considered Her-2/Neu overexpressed when staining resulted 3+ or 2+ with FISH amplification, negative if value was 0, 1+ or 2+ without FISH amplification. The following subtypes of breast cancer were considered in this study as previously defined: luminal A, luminal B, luminal Her, Her2-enriched, and triple-negative [26]. Moreover, the therapeutic management was investigated, including conservative versus radical, breast and axillary surgery, eventual neoadjuvant or adjuvant therapies.

Statistical analysis

Data was analyzed using R (version 3.0.1) and considering significant $P<0.05$. Data was presented where appropriate as mean (± standard deviation), median and interquartile range (IQR), proportions, or hazard ratio (HR) with relative 95% confidence interval. Univariate analysis was performed by t-test or Wilcoxon test in case of continuous variables, chi-square test or Fisher exact test in case of categorical variables. Overall survival (OS), disease-free survival (DFS), and loco-regional recurrences were also considered. Therefore, Kaplan-Meyer curves or cumulative events curves were drown to compare OS, DFS, and loco-regional recurrences among the four groups. Furthermore, Log-rank test, univariate, and multivariate Cox proportional hazards regression model analysis were performed.

Results

Patient characteristics and treatment

We analyzed data about 1013 women affected by invasive breast cancer with a mean age at diagnosis of 58.91 years (±12.35) and a median follow up of 49 months (30-69). In 580 cases the DCIS component was not found (group A), in 197 cases was minimal (group B),

Table 2. Tumor characteristics subdivided by intraductal component extension

	Not found (A)	Minimal (B)	Extended (C)	Prevalent (D)	
Histological type					
Ductal invasive carcinoma	79.8% (463/580)	88.3% (174/197)	89.0% (170/191)	88.9% (40/45)	(1, 2)
Lobular invasive carcinoma	12.2% (71/580)	4.6% (9/197)	5.2% (10/191)	2.2% (1/45)	(1, 2, 3)
Ductal and lobular invasive carcinoma	4.0% (23/580)	5.1% (10/197)	3.7% (7/191)	2.2% (1/45)	ns
Other invasive carcinoma	4.0% (23/580)	2% (4/197)	2.1% (4/191)	6.7% (3/45)	ns
Tumor characteristics					
ER positivity	85.3% (481/564)	87.7% (171/195)	85.8% (163/190)	63.6% (28/44)	(3, 5, 6)
PgR positivity	70.7% (399/564)	69.7% (136/195)	71.1% (135/190)	54.5% (24/44)	(3, 6)
Ki-67/Mib-1 >20	30.4% (165/543)	37.5% (72/192)	32.8% (60/183)	25% (4/16)	ns
Molecular Subtype					
Luminal A	55.5% (302/544)	48.4% (92/190)	48.9% (89/182)	27.8% (5/18)	(3)
Luminal B	24.6% (134/544)	31.1% (59/190)	28% (51/182)	11.1% (2/18)	ns
Luminal Her2	5.3% (29/544)	7.9% (15/190)	8.8% (16/182)	22.2% (4/18)	(3)
Her2 enriched	3.1% (17/544)	5.3% (10/190)	8.8% (16/182)	22.2% (4/18)	(2, 3, 5)
Basal-like	11.4% (62/544)	7.4% (14/190)	5.5% (10/182)	16.7% (3/18)	(2)
Comedo-like necrosis	0.5% (3/580)	17.3% (34/197)	27.7% (53/191)	40% (18/45)	(1, 2, 3, 4, 5)
Multifocality /multicentricity	13.6% (79/580)	17.3% (34/197)	25.1% (48/191)	24.4% (11/45)	(2, 3)
PVI	21.4% (124/580)	37.1% (73/197)	31.4% (60/191)	4.4% (2/45)	(1, 2, 3, 5, 6)
Peritunoral inflammation	0.9% (5/580)	0% (0/197)	1.6% (3/191)	0% (0/45)	ns
Lymph nodes characteristics					
Isolated tumor cells	1.7% (10/580)	0.5% (1/197)	1% (2/191)	2.2% (1/45)	ns
Micrometastases	5.2% (30/580)	6.1% (12/197)	3.7% (7/191)	6.7% (3/45)	ns
Extracapsular invasion of lymph node metastasis	8.8% (51/580)	14.2% (28/197)	11.5% (22/191)	0% (0/45)	(1, 3, 5, 6)
Bunched axillary lymph nodes	2.8% (16/580)	3% (6/197)	1% (2/191)	0% (0/45)	ns

Significant differences between: 1) Absent vs. Minimal; 2) Absent vs. Extended; 3) Absent vs. Prevalent; 4) Minimal vs. Extended; 5) Minimal vs. Prevalent; 6) Extended vs. Prevalent. (ns) = non significant.

in 191 cases was extensive (group C), and in 45 cases was prevalent (group D). In **Table 1** we show the characteristics of the population subdivided by DCIS component extension. In the case of extensive DCIS component (group C) the age at intervention was significantly lower than in group A where DCIS component was not found ($P<0.05$). A high extent of DCIS component (group C or groups C and D together) was significantly associated to an increased prevalence of familial history of breast cancer than group A or B ($P<0.05$). In group C and D we had the lowest prevalence of BCS as first line surgical treatment and as definitive treatment (**Table 1**). The prevalence of other treatment options is described in **Table 1** and, as expected, adjuvant treatments presented lower prevalence among the groups managed with higher rates of radical surgery.

Tumor characteristics and staging

Considering the whole population, the majority of cancers were ductal invasive carcinomas and this prevalence was significantly higher in group B or C than group A ($P<0.05$) (**Table 2**). As a consequence, the prevalence of invasive lobular carcinoma in group A was significantly higher than in group B, C, or D ($P<0.05$) (**Table 2**). In group D we found the significantly lowest prevalence of ER positivity ($P<0.05$) (**Table 2**). Furthermore, in groups C and D we found a high prevalence of luminal Her-2 and Her-2 enriched (**Table 2**). In addition, basal-like subtype was more common in group A than group C ($P<0.05$). Comedo-like necrosis presented a direct correlation with the amount of DCIS component extension and was significantly lower in group A than B, C, or D ($P<0.05$) (**Table 2**). Tumor multifocality/multicentricity was higher in group C and D than group A (**Table 2**). Moreover, among groups B, C, and D PVI was indirectly correlated with DCIS component extension as well as extracapsular invasion of lymph node metastasis (**Table 2**).

In **Table 3** we show the TNM staging of the tumor among the studied groups. We found in group D a higher prevalence of T1mic cancers and lower prevalence of T1 and T2 tumors than in the other groups ($P<0.05$) (**Table 3**). Group D showed the highest prevalence of N0 and TNM

Table 3. Tumor stage subdivided by intraductal component extension

	Not found (A)	Minimal (B)	Extended (C)	Prevalent (D)	
Tumor size					
T1m	0% (0/580)	0% (0/197)	0% (0/191)	93.3% (42/45)	(3, 5, 6)
T1	73.1% (424/580)	76.1% (150/197)	75.9% (145/191)	6.7% (3/45)	(3, 5, 6)
T2	21.4% (124/580)	19.8% (39/197)	23% (44/191)	0% (0/45)	(3, 5, 6)
T3	4.1% (24/580)	2.5% (5/197)	1% (2/191)	0% (0/45)	(2)
T4	1.4% (8/580)	1.5% (3/197)	0% (0/191)	0% (0/45)	ns
N					
N0	69.3% (402/580)	59.4% (117/197)	67% (128/191)	93.3% (42/45)	(1, 3, 5, 6)
N1	20.3% (118/580)	25.9% (51/197)	19.9% (38/191)	6.7% (3/45)	(3, 5, 6)
N2	5.2% (30/580)	9.6% (19/197)	9.9% (19/191)	0% (0/45)	(1, 2, 5, 6)
N3	5.2% (30/580)	5.1% (10/197)	3.1% (6/191)	0% (0/45)	ns
TNM stage					
I	56.2% (326/580)	52.8% (104/197)	54.5% (104/191)	91.1% (41/45)	(3, 5, 6)
II	29.5% (171/580)	31% (61/197)	30.9% (59/191)	6.7% (3/45)	(3, 5, 6)
III	12.4% (72/580)	13.7% (27/197)	13.1% (25/191)	0% (0/45)	(3, 5, 6)
IV	1.9% (11/580)	2.5% (5/197)	1.6% (3/191)	2.2% (1/45)	ns
Grading					
G1	23.1% (134/580)	24.4% (48/197)	20.4% (39/191)	6.7% (3/45)	(3, 5, 6)
G2	55% (319/580)	49.2% (97/197)	50.8% (97/191)	44.4% (20/45)	ns
G3	21.9% (127/580)	26.4% (52/197)	28.8% (55/191)	48.9% (22/45)	(3, 5, 6)

Significant differences between: 1) Absent vs. Minimal; 2) Absent vs. Extended; 3) Absent vs. Prevalent; 4) Minimal vs. Extended; 5) Minimal vs. Prevalent; 6) Extended vs. Prevalent. (ns) = non significant.

stage I, and when present, axillary nodal involvement was always micrometastatic. In addition, group D had a significant higher prevalence of G3 grading than groups A, B, or C. (P<0.05) (**Table 3**).

Overall and disease-free survival

In **Figure 1A** we show the overall survival among the studied groups, and it is possible to notice the higher survival rates of group D, even if the differences do not reach statistically significance. In **Figure 1B** we show the disease-free survival and the only difference closed to significance was between group B and group D (P=0.074). We further analyzed by univariate and multivariate Cox proportional hazards regression model the factors influencing disease-free survival. In **Table 4** we found a decreasing disease-free survival associated to a decrease of DCIS component extension. In particular, we found that, after multivariate correction, group B had a significant lower disease-free survival than group D (HR 5.61; 95% C.I. 1.06-29.62) (P<0.05) (**Table 4**). In addition, group B had a non-significant lower disease-free survival than group C (HR 1.33; 95% C.I. 0.56-3.18) (P=0.518). In **Figure 1C** we found a non-significant high prevalence of local recurrences in group B than groups C and D.

Discussion

From this study emerged an association of EIC (groups C and D) with luminal Her, Her-enriched, comedo-like necrosis, multifocality/multicentricity, high tumor grading, younger age, and familial history of breast cancer. Tumor PVI and extracapsular invasion of lymph node metastasis were more prevalent in patients with DCIS component (groups B and C) than in group A, and the amount of DCIS component resulted indirectly correlated with local recurrence rate, tumor PVI, and extracapsular invasion of lymph node metastasis. Group A had a higher prevalence of basal-like tumor subtype than group C. In addition, Cancers with prevalent DCIS component (group D) were mainly constituted by pT1mic tumors, and showed the highest survival rate, even without reaching statistical significance. On the other hand, the highest prevalence of local recurrences was found in case of

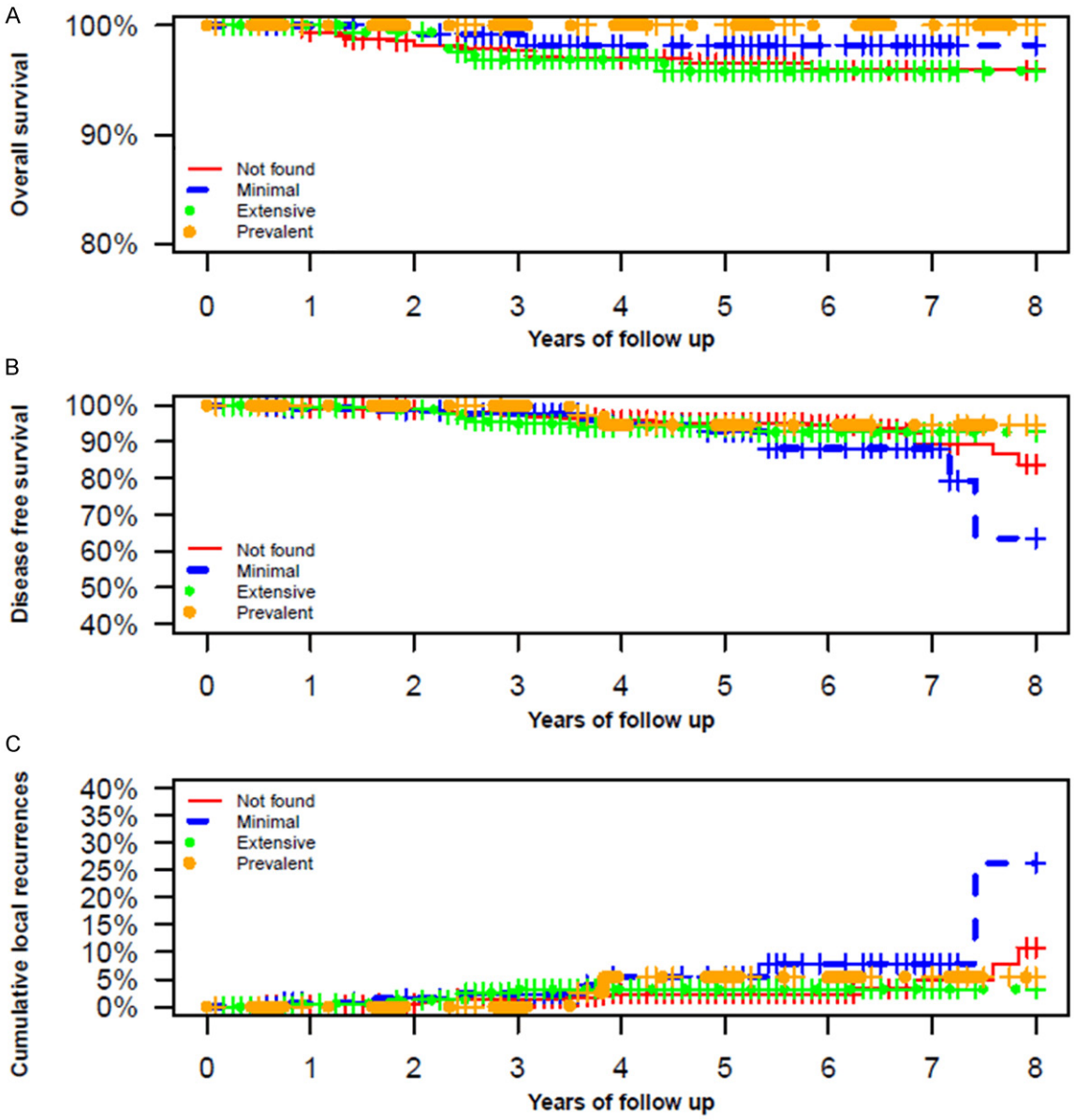

Figure 1. Kaplan-Meier and cumulative event curves: A: Overall-survival among studied groups; B: Disease-free survival among the studied groups; and C: Local recurrences among the studied groups.

minimal DCIS component (group B), which tended to be less frequently treated with radical surgery than groups D and C.

EIC is well recognized to be a risk factor for local recurrences in case of BCS [16], and some authors suggest to consider the proliferation activity of cancer cells in the DCIS component as one of the most important predictive factors of local recurrence in case of invasive breast cancer [17]. Our data show a significant correlation of DCIS component presence with many bad prognostic factors, which may also explain its strong recurrence trend.

For what concerns patients age, many studies demonstrated a correlation of EIC with young age and premenopausal status [14, 16, 17, 28-30], both conditions in which the DCIS component seems to have an intrinsically higher recurrence potential than in older patients [31]. In our population, if compared with cancers without an evident DCIS component, patients with EIC resulted to be significantly younger and

Table 4. Univariate and multivariate Cox proportional hazards regression model analysis

Intraductal component	HR (95% CI)	*P*	HR (95% CI)*	*P*
Group D (prevalent)	Reference	1.000	Reference	1.000
Group C (extended)	3.34 (0.72-15.43)	0.122	4.21 (0.83-21.25)	0.082
Group B (minimal)	3.80 (0.81-17.87)	0.091	5.61 (1.06-29.62)	<0.05
Group A (Not found)	2.38 (0.55-10.25)	0.245	2.93 (0.59-14.5)	0.187

*Multivariate analysis with correction for: TNM stage, grading, definitive surgery, comedo-like necrosis and tumor molecular Subtype.

to more frequently report familial history of breast cancer. Although in the literature BRCA genes mutations correlate with a lower prevalence of DCIS component than cancers not associated with mutations (59% vs 76%, p n.s.) [32], we can support our result with the recognized higher prevalence of familial history of breast cancer in young, premenopausal women [33].

Also the grade of concomitant DCIS [34], its multifocality/multicentricity [10-13], and the presence of eventual comedo-like necrosis [35] have been demonstrated to be predictive of an aggressive biological behavior and consequently of an unfavorable prognosis in patients with invasive breast carcinoma. And our data confirmed a significant correlation of DCIS component presence with high grade tumors, multifocality/multicentircity, and comedo-like necrosis.

Taking into consideration molecular subtypes, the literature has widely demonstrated that cancers which overexpress Her2/neu have the worst prognoses among invasive breast carcinomas, but there is very few data about molecular subtypes within the DCIS component of invasive cancers, because Her2/neu quantification does not currently represent a standard examination in case of DCIS. However, in our population we observed an increased prevalence of luminal Her-2, and Her-2-enriched subtypes among invasive breast cancers with DCIS component. These findings are in accordance with that recently published by Zhang et al. [36].

Despite the correlation of EIC with all this unfavorable prognostic factors, both in the literature and in our study population, our data showed EIC (groups C and D) to have a high overall survival rate and a low local recurrence rate. These encouraging results may be clearly explained by the high prevalence of definitive radical surgery in patient with EIC, probably due to the actual knowledge of EIC association with high recurrence rates after breast conservation. In contrast, in group B with minimal DCIS component, BCS had prevalence similar to group A and a DFS significantly lower than group D despite the adjustment for TNM stage. This could be also explained by the lower prevalence of definitive radical treatment in group B than group D or C.

In the literature it is found that breast cancer is a heterogeneous and complex disease, embracing several entities that have different histological features, risk factors, and clinical behavior [37]. Furthermore, it is though that in situ cancer is the precursor of all these heterogeneous invasive breast cancers. However, is situ breast cancer lacks a major feature that characterizes other cancers (eg cervix cancer); the fact that it has never been demonstrated that removal of the DCIS lesion reduces the subsequent incidence of invasive breast cancers [38]. From our study emerged that group A (no evidence of DCIS component) had different tumor characteristics than other groups with DCIS component. Also Zhang et al. found that microinvasive breast cancer associated with DCIS component and invasive breast cancer had different characteristics [36]. This suggests us to study the possible existence of a group of invasive breast cancers which could result from a direct transformation of ductal or lobular cells, and not originating from a pre-existing in situ neoplasia. In this perspective, considering only the group originating from a pre-existing in situ neoplasia the small invasive cancers with an abundant DCIS component (group D) may represent an initial stage of neoplastic infiltration process, while those with a minimal DCIS component (group B) may be the expression of an advanced stage of invasiveness. In fact, DCIS component amount resulted indirectly correlated with some histological characteristics of biological aggressiveness and advanced invasiveness, such as tumor PVI and extracapsular invasion of lymph node metastasis [39-41].

This interesting hypothesis about two possible origins of invasive breast carcinoma may also

explain the paradoxical higher local recurrence rate among patients with minimal intraductal component (group B), which are more frequently submitted to BCS despite their probable association with worse prognostic factors. Finally, our study lays the foundation for a further question to be developed in future research. In fact, an increased prevalence of local recurrences seems to be associated not only with EIC, but also with all those tumors (including group B) that have a minimal DCIS component, whose characterization and surgical management should be explored in the future.

The main limitation of the present study was the retrospective nature of this chart review analysis. In fact, the quantification of the in situ tumor component is not easy to define by the standard histological methods. First, because wide tumor samples are usually not completely analyzed by routinely methods allowing the possibility to miss the presence of the in situ tumor component. Second, because in situ tumor component could extend beyond the excised tumor lesion and could also be missed by pre-operative breast imaging work-up. In fact, in situ breast cancer is considered the precursor of the majority of invasive breast cancers while in this study we had a quite high proportion of samples in group A (without an in situ component) than in groups B, C, and D. However, in group A according to the literature we had a relative high prevalence of basal-like tumor subtype [1]. Furthermore, the prevalence of DCIS component and its groups of extension (groups B, C, and D) among our 1013 patients resulted comparable to that of a previous study on 250 women published by Elling and colleagues [14]. In particular, in our population a DCIS component was present in the 42.74% of cases, resulting minimal, extensive and prevalent respectively in the 19.45%, 18.85%, and 4.44%, while Elling and colleagues described a prevalence of in situ component of 50.8%, with a selective prevalence of minimal, extensive and predominant DICS respectively in the 14.0%, 31.2%, and 5.6% [14]. Another limitation of the present study is the limited follow up time with a median of 49 months. Anyway, in a previous study we found that the majority of recurrences were between 3 and 6 years [39] and in the present study more than 70% of the population had a follow up time longer than 3 years.

In summary, the presence of different clinical and tumor features between invasive breast cancer with and without DCIS component indicate that they are distinct entities probably originating from different pathways that deserve to be studied. In fact, our data suggested that invasive breast cancers with DCIS component probably originate from per-existing in situ neoplasia in young women with a family history of breast cancer, with biological characteristics of aggressiveness and high prevalence of local recurrence. Furthermore, in this study was found high disease recurrence in invasive breast cancer with minimal DCIS component that requires further studies in order to improve our knowledge and management.

Disclosure of conflict of interest

None.

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