Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Extensive Intraductal Component in Breast Cancer: What Role in Disease-Free Survival?

Fabio Corsi, MD,[a,b,*] *Sara Albasini, MSc,*[a] *Simone Ciciriello, MD,*[a] *Laura Villani, MD,*[c] *Marta Truffi, PhD,*[d] *Marta Sevieri, MSc,*[b] *and Luca Sorrentino, MD*[e]

[a] *Breast Unit, Department of Surgery, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[b] *Department of Biomedical and Clinical Sciences "Luigi Sacco", Università di Milano, Milan, Italy*
[c] *Department of Pathology, Istituto Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[d] *Nanomedicine and Molecular Imaging Lab, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[e] *Colorectal Surgery Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy*

ARTICLE INFO

Article history:
Received 7 February 2022
Received in revised form
27 September 2022
Accepted 17 October 2022
Available online 21 November 2022

Keywords:
Breast cancer
Disease-free survival
Extensive intraductal component
Local recurrence

ABSTRACT

Introduction: Extensive intraductal component (EIC) associated to early breast cancer could increase the risk locoregional recurrence, but its impact on distant metastases is still unclear. The aim of the present study was to assess the role of EIC on 5-year survival outcomes in patients affected by early breast cancer treated with breast-conserving surgery.
Methods: A total of 414 consecutive patients with a minimum follow-up of 60 mo were collected from January 2007 to December 2015. Disease-free survival (DFS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival at 5 y were assessed considering the presence or absence of EIC and other clinical and pathological features.
Results: Absence of EIC was independently associated with worse 5-year DFS (hazard ratio [HR] 1.68, $P = 0.008$) and 5-year DMFS (HR 1.93, $P = 0.007$), whereas 5-year locoregional recurrence-free survival was not affected (HR 1.50, $P = 0.16$). Five-year DFS was increased by EIC in T1 patients ($P = 0.03$) but not in T2 stage. Moreover, EIC was associated to better DFS in G2 ($P = 0.03$) and G3 patients ($P = 0.01$) but not in G1 cases.
Conclusions: Our results suggest that EIC is independently correlated with increased 5-year DFS and in particular with 5-year DMFS.

Introduction

Ductal carcinoma *in situ* (DCIS) of the breast is a nonobligate precursor of invasive breast cancer, accounting for 20% of screening-detected breast lesions.[1,2] DCIS associated to invasive cancer, named extensive intraductal component (EIC), is a well-known recognized risk factor for positive margins after breast-conserving surgery and for local relapses, rising up to 26% if EIC is observed on final pathology.[3,4] Not only EIC is not palpable nor directly detectable by the operating surgeon during excision but invasive breast cancer with EIC is also most frequently prone to discrepancies between clinical size estimated on preoperative imaging, preoperative localization, and the pathological tumor size.[5,6] Furthermore, in case of EIC

* *Corresponding author*. Department of Biomedical and Clinical Sciences "Luigi Sacco", Università di Milano, Via G. B. Grassi, 74, 20157 Milan, Italy, Surgery Department, Breast Unit, ICS Maugeri S.p.A. SB, via Maugeri 10, 27100 Pavia, Italy. Tel.: +39 02 5031 9850.
E-mail address: fabio.corsi@unimi.it (F. Corsi).
0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2022.10.094

associated to early breast cancer, cavity shave of margins together with lumpectomy has been suggested by the American Society of Breast Surgeons, remarking that EIC is associated to a high risk of positive margins.[7] Therefore, it would be expected that EIC reduces long-term survival, by increasing the risk of locoregional recurrences.[8,9] However, its impact on survival is currently unclear because evidences suggest no role of EIC on survival, whereas other studies indicate even an unexpected improvement on long-term outcomes.[10,11] This could be explained by a biological distinction between pure invasive cancer with and without EIC because the former probably represents a tumor which is still evolving from DCIS into invasive ductal cancer, thus expectedly less aggressive.[12] The impact of EIC on survival in different biomolecular subtypes and pathological stages is even less clear, and long-term survival data are lacking. However, the presence of EIC at final pathology might be informative both on local relapse and distant metastasis risk and disease-free survival. The aim of the present study was to assess the role of EIC on 5-year survival outcomes in patients affected by early invasive breast cancer treated with breast-conserving surgery.

Methods and Materials

Study population

Patients were retrospectively collected from the prospectively maintained database of the EUSOMA-accredited Breast Unit of ICS Maugeri Hospital, from January 2007 to December 2015. The study protocol was approved by the Ethical Committee of the Institution (VONEMA protocol, approval number 2590CE) and a signed informed consent was obtained and stored for every enrolled patient. Inclusion criteria were proven diagnosis of invasive breast cancer, undergoing breast-conserving surgery in first instance, radiotherapy and adjuvant treatments with curative intent, negative margins status at final pathology after surgery, and a minimum follow-up of 60 mo. Patients with involved or close margins at the final pathology were excluded. Patients with benign lesions or pure DCIS, T3-T4 carcinoma requiring total mastectomy, distant metastases at diagnosis, palliative treatment, a previous diagnosis of breast or other solid malignancies, neoadjuvant chemotherapy, or with relevant data missing were excluded from the study.

Study design and end points

Included patients were divided in two groups based on presence *versus* absence of EIC, defined as the observation of intraductal carcinoma in more than 25% of the total tumor on final pathology.[13] Every tumor specimen was observed and evaluated by the same pathologist, who scored the percentage of EIC on the most representative samples for each patient. The extension of EIC, expressed as its percentage within invasive cancer on representative slices, was reported. Locoregional recurrence (LRR) was defined as the occurrence of a biopsy-proven ipsilateral breast cancer and/or axillary relapse, whereas distant metastasis (DM) was defined as the evidence of distant lesions on imaging (computed tomography and positron emission tomography), with features suggesting distant relapses, even if not histologically proven. The distribution of all relevant clinical and pathological variables was assessed between these two groups. Then, multivariate analyses were performed to assess the independent impact of EIC on long-term disease-free survival (DFS) and to rule out other independent predictors. Finally, the prognostic role of EIC was assessed in different categories of each significant predictor of survival, by stratifying presence *versus* absence of EIC in specific Kaplan–Meier curves. All the main clinical and pathological variables (pT stage, pN stage, grading, biomolecular subtype, etc.) between patients with and without EIC were balanced, thus a matching technique was not considered necessary. Furthermore, matching techniques (e.g., propensity score matching) are correctly applied to variables ideally measured prior to the exposure (i.e., preoperatively known variables only measured before detecting EIC, exposure in this case) to avoid accidently adjusting for potential mediators.[14] Postoperatively known variables have been therefore taken into account by multivariate regression.

The primary end point of the study was the 5-year DFS in breast cancer patients treated with breast-conserving surgery, with or without EIC. Secondary end points were (1) the 5-year LRR-free (LRRFS) and DM-free survivals (DMFS) with and without EIC and (2) the prognostic role of EIC on 5-year DFS in the context of specific other independent predictors of survival.

Statistical analysis

Differences between patients with and without EIC were assessed to verify the heterogeneity of the study population. Variables were reported as means and standard deviations or as absolute numbers and percentages. Categorical variables were compared using χ^2 test or Fisher's exact test when sample size was less than or equal to 5, whereas continuous variables were compared using Student's *t*-test or nonparametric Wilcoxon test in case of non-normal distribution of the variable. To identify possible effects of each variable significantly associated with the events (LRR, DM, or any first event) in a time-dependent setting, a Cox proportional hazard regression model was performed, after verifying the proportional hazard assumption of the model. The 5-year DFS, LRR-free, and DM-free survival probabilities were estimated by the Kaplan–Meier method both globally and in specific subsets. Statistical significance was set at $P < 0.05$ (two-tailed). Data analysis was performed using SAS software (v. 9.4, SAS Institute Inc, Cary).

Results

Baseline characteristics between patients with or without extensive intraductal component

A total of 414 consecutive patients with a minimum follow-up of 60 mo (mean 81 mo, standard deviation 35) were included in the study: in 166 cases (40.1%) EIC was observed, whereas in the remaining 248 cases (59.9%) no EIC was found at final pathology. Patients with EIC were younger (56 *versus* 60 y,

$P = 0.003$), characterized by a higher proportion of ductal histological type (85.5% *versus* 75.0%, $P = 0.03$), and a smaller pathological tumor size (11.9 *versus* 14.6 mm, $P < 0.0001$). All the other characteristics, in particular adjuvant treatments (radiotherapy, hormone therapy, and chemotherapy), were balanced between the two groups, as reported in Table 1.

Survival analyses

Administration of radiotherapy ($P = 0.28$), hormone therapy ($P = 0.28$), and chemotherapy ($P = 0.63$) was balanced between the two groups of patients, as reported in Table 1. In HER2-positive breast cancer, anti-HER2 monoclonal antibody was administered in 96.0% of EIC patients *versus* 80.0% of cases without EIC ($P = 0.20$), as reported in Supplementary Table S1. At 5 y, 45 patients experienced local recurrence only, 63 patients experienced distant metastasis only, and 20 patients experienced both of them. DM were detected in 15.0% of EIC patients *versus* 28.4% of cases without EIC ($P = 0.003$), while no difference was observed in LRR rate ($P = 0.17$), as reported in Table 2. Patients with EIC showed an improved 5-year DFS compared to those without EIC (75.3% *versus* 62.1%, Log-rank $P = 0.006$), as reported in Figure 1. EIC was also associated with increased 5-year DMFS (85% *versus* 71.6 %, Log-rank $P = 0.003$), as reported in Figure 2. Conversely, no difference between presence and absence of EIC was observed on LRRFS (Log-rank $P = 0.18$), as reported in Figure 3. Kaplan–Meier curves for LRRFS seemed to overlap in the early period of follow-up, so we tested the proportional hazard assumption of the model and it was accepted ($P = 0.73$). DMFS and DFS curves had basically the same shape, did not cross, and started close and then diverged slowly through follow-up time, so proportional hazard assumption was verified.

Independent prediction of EIC and other features on DFS, LRRFS, and DMFS

Proportional hazard assumption was accepted for DFS, LRRFS, and DMFS Cox regression model ($P = 0.79$, $P = 0.41$, and $P = 0.20$, respectively). On multivariate Cox regression analysis, absence of EIC was independently associated with worse 5-year DFS (hazard ratio [HR] 1.68, 95% confidence interval [CI] 1.14-2.48, $P = 0.008$) and 5-year DMFS (HR 1.93, 95% CI 1.16-3.22, $P = 0.01$), while 5-year LRRFS was not affected by EIC (HR 1.50, 95% CI 0.86-2.61, $P = 0.16$). Main independent predictors for worse DFS were G2 and G3 grading in comparison with G1 (HR 3.30, $P = 0.006$ and HR 2.94, $P = 0.03$, respectively), other nonductal nonlobular histological types (HR 2.49, $P = 0.02$), pN2-3 stage (HR 2.13, $P = 0.004$), and not receiving radiotherapy nor hormone therapy (HR 2.26, $P = 0.001$ and HR 2.33, $P = 0.003$, respectively). Similar predictive factors were observed for DMFS, except for radiotherapy that was not statistically significant. Conversely, the only negative predictive features found for LRRFS were ER-/HER2-subtype (HR 3.55, $P = 0.03$), lacking of radiotherapy (HR 3.03, $P = 0.007$), chemotherapy (HR 3.94, $P = 0.004$), or hormone therapy (HR 3.40, $P = 0.002$), as reported in Table 3. For each significant predictor of DFS, presence of EIC identified a subset of patients with an improved DFS, as observed in Supplementary Figures S1-S4. Five-year DFS was increased by EIC in T1 patients (Log-rank $P = 0.03$) but not in T2 stage (Log-rank $P = 0.32$). Furthermore, EIC was associated to better DFS in G2 (Log-rank $P = 0.03$) and G3 patients (Log-rank $P = 0.01$) but not in G1 cases (Log-rank $P = 0.47$). EIC was not a relevant predictor of better DFS when each biomolecular subtype of breast cancer was considered separately nor among pN0 patients (Log-rank $P = 0.08$), while a trend toward higher DFS with EIC was observed in pN + patients (Log-rank $P = 0.05$).

Discussion

Predictive and prognostic factors like hormone receptor status and HER2/neu overexpression are guiding our therapeutic behavior, but among the same subsets of patients' different outcomes are still observed, suggesting that other features might stratify the recurrence risk.[15] Such patients' stratification would allow to enhance or de-escalate adjuvant treatments and follow-up strategies. Novel promising approaches, such as liquid biopsy or genomics, have been proposed in recent years but their wide feasibility and cost-effectiveness are still questionable in several institutions.[16,17] Easily gettable prognostic features might therefore be useful in refinishing the prognostication of early breast cancer patients.

Some studies have suggested that presence of EIC has an independent prognostic value.[8] In the present study, breast cancer patients with an associated EIC showed a 5-year DFS strongly improved compared to patients without EIC, respectively, 75.3% *versus* 62.1% ($P = 0.005$), and a significantly increased DMFS (85% *versus* 71.6 %, respectively, $P = 0.003$). Moreover, despite the presence of an EIC has traditionally been considered a negative prognostic factor for local recurrence in a breast conservative setting, in the present cohort LRRFS rates were similar between the two groups ($P = 0.18$).

A possible explanation for these findings is that locoregional recurrence is currently a rare event in breast cancer: hormone therapy, preoperative localization, routine cavity shave of margins, and breast radiotherapy, considered a standard of care, have all decreased the occurrence of local relapse. One of our inclusion criteria was negative margins status at final pathology after surgery; however, the positive margins rate is particularly low in our Institute, since preoperative localization[18-20] and cavity shave of all margins during lumpectomy[21] are routinely performed in all patients. Therefore, the risk of residual *in situ* disease in the remnant breast after lumpectomy is generally low; thus, in the era of modern multimodal treatment of breast cancer, EIC should not be more considered a predictor of local failure.[11,22] Furthermore, EIC is known to impact on local recurrence rate in case of positive margins, but in the present cohort of patients, margins status was negative on final pathology in all cases. Conversely, presence of EIC associated to invasive cancer might suggest an initial stage of breast cancer, representing the beginning of progression from *in situ* to invasive cancer, thus possibly being a less aggressive disease.[11,12,22] Therefore, long-term survival, depending on occurrence of distant metastases, was increased in case of EIC. In recent literature it has increasingly emerged as a "protective" role of EIC for DFS, probably because the presence of EIC represents a more "benign" disease compared to pure invasive breast cancer,

Table 1 – Distribution of baseline variables in the study population ($n = 414$).

Variable	Extensive intraductal component (EIC)		
	Not evident ($n = 248$)	Present ($n = 166$)	P value
Age at diagnosis (y)	60 (± 12.5)	56 (± 12.0)	0.003
Multifocal disease			
No	227 (91.5%)	127 (76.5%)	0.14
Yes	21 (8.5%)	39 (23.5%)	
Bilateral disease			
No	264 (96.6%)	80 (96.3%)	1
Yes	9 (3.4%)	3 (3.7%)	
Histological type			
Ductal	186 (75%)	142 (85.5%)	0.03
Lobular	46 (18.6%)	16 (9.6%)	
Others	16 (6.4%)	8 (4.9%)	
Grading			
G1	43 (17.4%)	25 (15.2%)	0.49
G2	132 (53.4%)	98 (59.4%)	
G3	72 (29.2%)	42 (25.5%)	
Lymphovascular invasion			
No	169 (68.2%)	118 (72%)	0.41
Yes	79 (31.9%)	46 (28.1%)	
Pathological tumor size (mm)	14.6 (± 6.8)	11.9 (± 6.3)	< 0.0001
pT stage			
pT1	210 (84.7%)	151 (91.0%)	0.072
pT2	38 (15.3%)	15 (9%)	
pN stage			
pN0	167 (67.3%)	118 (71.1%)	0.63
pN1mic	3 (1.2%)	0 (0%)	
pN1	51 (20.6%)	35 (21.1%)	
pN2	14 (5.7%)	7 (4.2%)	
pN3	13 (5.2%)	6 (3.6%)	
ER			
Negative	42 (16.9%)	27 (16.3%)	0.86
Positive	206 (83.1%)	139 (83.7%)	
PG			
Negative	56 (22.6%)	38 (22.9%)	0.94
Positive	192 (77.4%)	128 (77.1%)	
HER2			
Negative	219 (89.8%)	141 (84.9%)	0.14
Positive	25 (10.3%)	25 (15.1%)	
Ki67			
≤14%	146 (58.9%)	109 (65.7%)	0.16
>14%	102 (41.1%)	57 (34.3%)	
Biomolecular subtype			
ER+/Her2-	192 (78.7%)	128 (77.1%)	0.35
ER+/Her2+	13 (5.3%)	11 (6.6%)	
ER-/Her2-	27 (11.1%)	13 (7.8%)	
ER-/Her2+	12 (4.9%)	14 (8.4%)	
Radiotherapy			
No	31 (12.5%)	27 (16.3%)	0.28
Yes	217 (87.5%)	139 (83.7%)	
Chemotherapy			
No	154 (62.1%)	107 (64.5%)	0.63
Yes	94 (37.9%)	59 (35.5%)	
Hormone therapy			
No	59 (23.8%)	32 (19.3%)	0.28
Yes	189 (76.2%)	134 (80.7%)	
Percentage of EIC associated to invasive cancer			
25%-50%	-	101 (60.8%)	-
50%-75%	-	37 (22.3%)	
>75%	-	28 (16.9%)	

accordingly to the findings of the present study.[22-24] However, the specific role of EIC on survival in patients with negative margins status only after breast-conserving surgery has been previously poorly explored.

On multivariate Cox analysis, absence of EIC was confirmed to independently predict a worse 5-year DFS (HR 1.68, $P = 0.008$) and DMFS (HR 1.93, $P = 0.01$). Since other classical predictors emerged from Cox analyses, such as grading, pT, and pN stage, EIC was specifically assessed in each category for these variables, to assess if EIC could predict DFS in patients irrespectively from staging and grading. On Kaplan–Meier curves, EIC confirmed to be a strong predictor of improved DFS in T1 ($P = 0.03$) but not in T2 cancers ($P = 0.32$), probably because in T2 cancers EIC is poorly represented, due to the greater pathological size of the invasive component; thus, the disease is expected to be more aggressive. EIC predicted better DFS also in G2 ($P = 0.03$) and G3 ($P = 0.01$) cancers but not in G1 ($P = 0.47$) because the latter lesions have

Table 2 – Crude event rates.

Variable	Extensive intraductal component			
	Not evident ($n = 248$)	Present ($n = 166$)	Total	P value
Distant metastases				
No	154 (71.6%)	125 (85%)	279	0.003
Yes	61 (28.4%)	22 (15%)	83	
Locoregional recurrence				
No	154 (78.6%)	125 (84.5%)	279	0.17
Yes	42 (21.4%)	23 (15.5%)	65	
Any first event				
No	154 (62.1%)	125 (75.3%)	279	0.005
Yes	94 (37.9%)	41 (24.7%)	135	

generally an indolent course *per se*, thus presence or absence of EIC is irrelevant to define prognosis. EIC did not affect survival considering each biomolecular subtype nor in pN0 patients, despite a trend toward significance was observed for pN + cases, where presence of EIC again predicted an improved DFS ($P = 0.05$).

The present study has some major limitations. First, its retrospective nature implies that presented data rely on pathologic reports after primary surgery, without any direct reassessment of surgical specimens. However, all specimens were sampled as per standard guidelines. Three categories were considered based on percentage of EIC, as previously reported and widely accepted: 25%-50%, 50%-75%, and > 75%.[13] Therefore, the evaluation of EIC was performed in a standardized way and easily reviewed from pathological reports. An important aspect is that genomic profiling has drawn interest in the field, especially to investigate key factors of DCIS progression to invasive carcinoma, where genetic alterations are generally considered to be the potential main triggers, or to identify prognostic factors of DCIS relapse.[25-28] However, to our knowledge, a guide on genomic testing is currently not available in standard clinical practice and therefore has not been included in our study for analysis of survival. Based on the retrospective nature of our study and on the fact that cases were unselected, we did not include any genomic analysis in the evaluation of the study population.

Another limitation is the long time period of the study and the possible changes in guidelines could have led to different treatments of such patients impacting on prognosis. To overcome this bias, a regression model was performed considering all possible confounders, including received treatments (radiotherapy, hormone therapy, and chemotherapy), despite they were balanced between groups. Anyway, further studies with larger populations will be needed to reveal more robust data.

Clinically compliant predictors of outcomes are highly desired in breast cancer because genomic testing is not routinely available in all Breast Units, especially in low-to-middle income countries. Biomolecular subtype and pTNM stages are standard predictors and guide adjuvant treatments, but the present work demonstrates that EIC is an independent predictor of both distant metastases-free and disease-free survival. Therefore, it could be a useful feature to be evaluated during multidisciplinary decisions on adjuvant

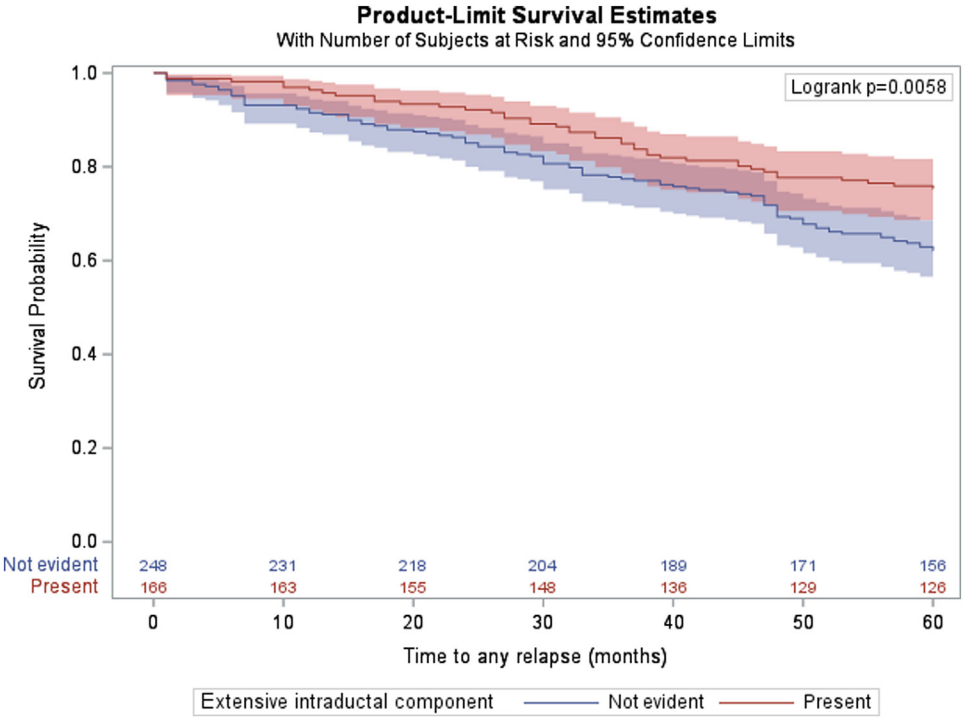

Fig. 1 – Kaplan–Meier curves for disease-free survival.

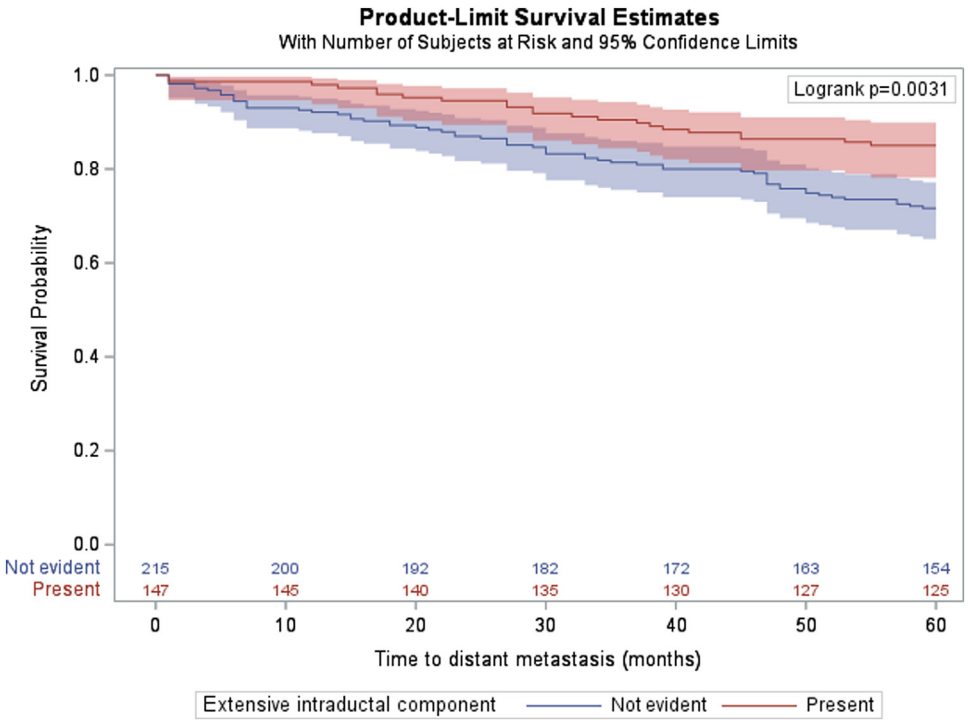

Fig. 2 – Kaplan–Meier curves of distant metastases-free survival.

treatments in the attempt to personalize treatments also in Breast Units where innovative techniques such as genomic testing is not available to predict the recurrence risk. In particular, the findings of the present study suggest that in patients affected by pT1, G2-G3 breast cancer with EIC, de-escalation of adjuvant treatments might be reasonably

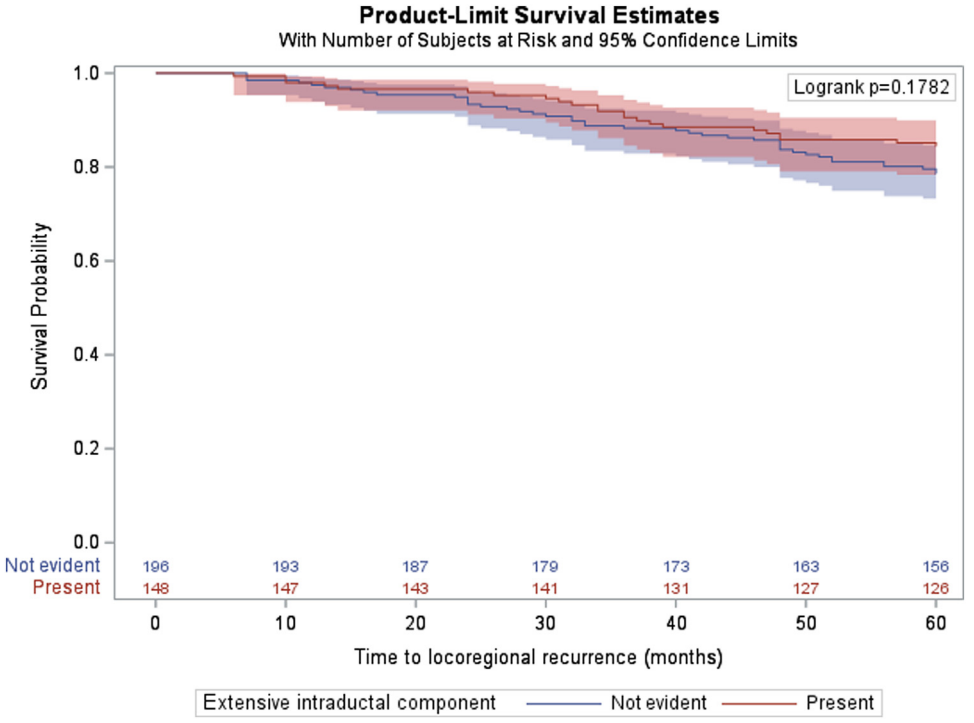

Fig. 3 – Kaplan–Meier curves of locoregional recurrence-free survival.

Table 3 – Cox proportional hazard regression model.

Variable	5-year DMFS			5-year LRRFS			5-year DFS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Extensive intraductal component									
Not evident	1.93	(1.16-3.22)	0.01	1.50	(0.86-2.61)	0.16	1.68	(1.14-2.48)	0.008
Present	-	-	-	-	-	-	-	-	-
Histological type									
Ductal	1.52	(0.75-3.09)	0.25	1.09	(0.48-2.47)	0.84	1.20	(0.70-2.03)	0.51
Others	3.33	(1.17-9.46)	0.02	2.01	(0.59-7.01)	0.27	2.49	(1.13-5.46)	0.02
Lobular	-	-	-	-	-	-	-	-	-
Grading									
G2	5.99	(1.41-24.48)	0.01	2.62	(0.89-7.68)	0.08	3.30	(1.40-7.77)	0.006
G3	5.57	(1.18-26.27)	0.03	2.91	(0.79-10.07)	0.11	2.94	(1.11-7.78)	0.03
G1	-	-	-	-	-	-	-	–	-
Lymphovascular invasion									
Present	1.41	(0.84-2.39)	0.19	1.32	(0.74-2.38)	0.35	1.35	(0.91-2.00)	0.13
Not evident	-	-	-	-	-	-	-	-	-
pT stage									
pT2	1.82	(1.09-3.01)	0.02	1.06	(0.46-2.47)	0.88	1.54	(0.99-2.39)	0.05
pT1	-	-	-	-	-	-	-	-	-
pN stage									
pN2/3	2.57	(1.40-4.70)	0.002	2.07	(0.83-5.21)	0.12	2.13	(1.26-3.59)	0.004
pN0/1mic/1	-	-	-	-	-	-	-	-	-
Ki67									
>14%	1.33	(0.77-2.29)	0.31	2.01	(1.01-4.00)	0.05	1.55	(1.00-2.40)	0.05
≤14%	-	-	-	-	-	-	-	-	-
Biomolecular subtype									
ER+/Her2+	0.49	(0.18-1.35)	0.17	1.89	(0.50-7.21)	0.35	0.69	(0.30-1.62)	0.40
ER-/Her2+	0.39	(0.14-1.12)	0.08	1.43	(0.40-5.03)	0.58	0.62	(0.26-1.47)	0.28
ER-/Her2-	0.91	(0.35-2.40)	0.85	3.55	(0.13-11.12)	0.03	1.39	(0.62-3.07)	0.43
ER+/Her2-	-	-	-	-	-	-	-	-	-
Radiotherapy									
No	1.88	(0.88-4.01)	0.10	3.03	(1.59-5.76)	0.007	2.26	(1.39-3.66)	0.001
Yes	-	-	-	-	-	-	-	-	-
Chemotherapy									
No	0.73	(0.38-1.40)	0.34	3.94	(1.57-9.89)	0.004	1.03	(0.61-1.75)	0.91
Yes	-	-	-	-	-	-	-	-	-
Hormonotherapy									
No	2.97	(1.45-6.08)	0.003	3.40	(1.55-7.44)	0.002	2.33	(1.33-4.08)	0.003
Yes	-	-	-	-	-	-	-	-	-

discussed, especially when the multidisciplinary decision is not unanimous.

Conclusions

EIC seems to be independently correlated with increased 5-year DFS and DMFS. In the era of multimodal treatment of breast cancer, EIC should not be considered reductively as a risk factor for local relapse and they should be evaluated more broadly.

EIC should be therefore carefully taken into account not to modify the surgical approach but to stratify the risk of distant relapses to guide the follow-up management.

Supplementary Materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jss.2022.10.094.

Author Contributions

Fabio Corsi: Conception and design of the study and interpretation of data. Sara Albasini: Analysis and interpretation of data. Simone Ciciriello: Acquisition of data. Laura Villani: Design of the study. Marta Truffi: Design of the study. Marta Sevieri: Design of the study. Luca Sorrentino: Conception and design of the study and interpretation of data.

Disclosure

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. van Steenbergen LN, Voogd AC, Roukema JA, et al. Screening caused rising incidence rates of ductal carcinoma in situ of the breast. *Breast Cancer Res Treat*. 2009;115:181–183.
2. Glover JA, Bannon FJ, Hughes CM, et al. Increased diagnosis and detection rates of carcinoma in situ of the breast. *Breast Cancer Res Treat*. 2012;133:779–784.
3. Jacquemier J, Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. An assessment of extensive intraductal component as a risk factor for local recurrence after breast-conserving therapy. *Br J Cancer*. 1990;61:873–876.
4. Boyages J, Recht A, Connolly JL, et al. Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol*. 1990;19:29–41.
5. Di Pasquale Guadalupe L, De Jesús J, Xiong Y, Rosa M. Tumor size and focality in breast carcinoma: analysis of concordance between radiological imaging modalities and pathological examination at a cancer center. *Ann Diagn Pathol*. 2020;48:151601.
6. Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. *N Engl J Med*. 2004;350:1430–1441.
7. McEvoy MP, Landercasper J, Naik HR, Feldman S. Update of the American Society of breast surgeons toolbox to address the lumpectomy reoperation epidemic. *Gland Surg*. 2018;7:536–553.
8. Espina V, Liotta LA. What is the malignant nature of human ductal carcinoma in situ? *Nat Rev Cancer*. 2011;11:68–75.
9. Chagpar AB, McMasters KM, Sahoo S, Edwards MJ. Does ductal carcinoma in situ accompanying invasive carcinoma affect prognosis? *Surgery*. 2009;146:561–567.
10. Ha SM, Cha JH, Shin HJ, Chae EY, Choi WJ, Kim HH. Mammography, US, and MRI to assess outcomes of invasive breast cancer with extensive intraductal component: a matched cohort study. *Radiology*. 2019;292:299–308.
11. Kole AJ, Park HS, Johnson SB, Kelly JR, Moran MS, Patel AA. Overall survival is improved when DCIS accompanies invasive breast cancer. *Sci Rep*. 2019;9:9934.
12. Wong H, Lau S, Yau T, Cheung P, Epstein RJ. Presence of an in situ component is associated with reduced biological aggressiveness of size-matched invasive breast cancer. *Br J Cancer*. 2010;102:1391–1396.
13. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy. *Cancer*. 1984;53:1049–1057.
14. ShibaK, Kawahara T. Using propensity scores for causal inference: pitfalls and tips. *J Epidemiol*. 2021;31:457–463.
15. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351:2817–2826.
16. Matsutani A, Udagawa C, Matsunaga Y, Nakamura S, Zembutsu H. Liquid biopsy for the detection of clinical biomarkers in early breast cancer: new insights and challenges. *Pharmacogenomics*. 2020;21:359–367.
17. Markopoulos C, Hyams DM, Gomez HL, et al. Multigene assays in early breast cancer: insights from recent phase 3 studies. *Eur J Surg Oncol*. 2020;46:656–666.
18. Corsi F, Sorrentino L, Sartani A, et al. Localization of nonpalpable breast lesions with sonographically visible clip: optimizing tailored resection and clear margins. *Am J Surg*. 2015;209:950–958.
19. Corsi F, Bossi D, Combi F, et al. Radio-guided vs clip-guided localization of nonpalpable mass-like lesions of the breast from a screened population: a propensity score-matched study. *J Surg Oncol*. 2019;119:916–924.
20. Corsi F, Bossi D, Sartani A, et al. Radio-guided and clip-guided preoperative localization for malignant microcalcifications offer similar performances in breast-conserving surgery. *Breast J*. 2019;25:865–873.
21. Corsi F, Sorrentino L, Bonzini M, et al. Cavity shaving reduces involved margins and reinterventions without increasing costs in breast-conserving surgery: a Propensity Score-Matched Study. *Ann Surg Oncol*. 2017;24:1516–1524.
22. Carabias-Meseguer P, Zapardiel I, Cusidó-Gimferrer M, et al. Influence of the in situ component in 389 infiltrating ductal breast carcinomas. *Breast Cancer*. 2013;20:213–217.
23. Wu SG, Zhang WW, Sun JY, He ZY. Prognostic value of ductal carcinoma in situ component in invasive ductal carcinoma of the breast: a Surveillance, Epidemiology, and End Results database analysis. *Cancer Manag Res*. 2018;10:527–534.
24. Lopez Gordo S, Blanch Falp J, Lopez-Gordo E, Just Roig E, Encinas Mendez J, Seco Calvo J. Influence of ductal carcinoma in situ on the outcome of invasive breast cancer. A prospective cohort study. *Int J Surg*. 2019;63:98–106.
25. Nagasawa S, Kuze Y, Maeda I, et al. Genomic profiling reveals heterogeneous populations of ductal carcinoma in situ of the breast. *Commun Biol*. 2021;4:438.
26. Young KS, Hyun JS, Sung KM, et al. Genomic differences between pure ductal carcinoma in situ and synchronous ductal carcinoma in situ with invasive breast cancer. *Oncotarget*. 2015;6:7597–7607.
27. Doebar SC, Sieuwerts AM, de Weerd V, Stoop H, Martens JWM, van Deurzen CHM. Gene expression differences between ductal carcinoma in situ with and without progression to invasive breast cancer. *Am J Pathol*. 2017;187:16481655.
28. Hernandez L, Wilkerson PM, Lambros MB, et al. Genomic and mutational profiling of ductal carcinomas in situ and matched adjacent invasive breast cancers reveals intra-tumour genetic heterogeneity and clonal selection. *J Pathol*. 2012;227:42–52.