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Microcalcifications matter: Diagnostic and biological differences in DCIS

Luca Nicosia [a,*], Luciano Mariano [a], Carmen Mallardi [b], Filippo Pesapane [a], Lorenza Meneghetti [a], Francesca Abbate [a], Samuele Frassoni [c,d], Vincenzo Bagnardi [c], Cristian Gialain [e], Giovanni Corso [f,g], Nicola Fusco [g,h], Enrico Cassano [a]

[a] Division of Breast Radiology, Department of Medical Imaging and Radiation Sciences, IEO European Institute of Oncology, IRCCS, 20141, Via Ripamonti 435, Milano, Italy
[b] Postgraduation School in Radiodiagnostics, Università degli Studi di Milano, Via Festa del Perdono, 7, 20122 Milan, Italy
[c] Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[d] Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
[e] Clinical Trial Office, IEO European Institute of Oncology IRCCS, 20141 Milan, Italy
[f] Division of Breast Surgery, European Institute of Oncology IEO, IRCCS, Milan, Italy
[g] Department of Oncology and Hematology, University of Milano, Milan, Italy
[h] Division of Pathology, IEO, European Institute of Oncology IRCCS, Via G. Ripamonti 435, 20141, Milan, Italy

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ABSTRACT

Introduction: Ductal carcinoma in situ (DCIS) is a non-invasive breast cancer increasingly detected through screening. While microcalcifications are the most common feature, a subset lacks them, posing diagnostic and management challenges. We investigated the relationship between radiological presentation (calcified vs. non-calcified) and the risk of upstaging to invasive carcinoma.

Materials and Methods: We retrospectively analyzed 196 patients with biopsy-proven DCIS who underwent surgery between 2000 and 2023. Ninety-eight (98) non-calcified cases diagnosed via ultrasound-guided vacuum-assisted biopsy were matched with 98 calcified cases diagnosed via stereotactic vacuum-assisted biopsy, based on age, grade, and macroscopic removal. We investigated the associations between upstaging and potential predictors, including calcification status, age at biopsy, lesion size, and histologic grade at biopsy.

Results: The overall underestimation rate was 13.8% (27/196). Non-calcified DCIS showed a higher upstaging rate than calcified DCIS (19% vs. 8%; multivariable OR for calcified DCIS: 0.31, 95% CI: 0.12–0.78, $p = 0.013$). Larger lesions increased the risk of underestimation (OR per 5 mm: 1.21, 95% CI: 1.06–1.38, $p = 0.005$), while age was not significant (OR per 5 years: 1.01, $p = 0.91$).

Conclusions: Non-calcified DCIS and larger lesion size seemed independently associated with upstaging to invasive carcinoma, highlighting the clinical relevance of radiological presentation for risk stratification.

Introduction

Ductal carcinoma in situ (DCIS) represents one of the earliest detectable forms of breast cancer (BC), histologically characterized by the proliferation of malignant epithelial cells confined within the mammary ductal system, without invasion into the surrounding stromal tissue [1,2]. In recent decades, its incidence has increased significantly, mainly due to the widespread implementation of population-based mammographic screening programs [2]. In contemporary screening settings, DCIS accounts for approximately 20–25% of all BC diagnoses in high-income countries, reflecting both heightened public awareness and improved imaging sensitivity [3]. Despite its non-invasive nature, DCIS poses significant clinical management challenges, mainly due to its biological heterogeneity and unpredictable natural history [4,5]. While some cases may progress to become invasive BC, many remain indolent and clinically silent [6]. However, current therapeutic approaches are not yet able to reliably discriminate between indolent and progressive disease, often resulting in overtreatment [7,8]. Standard treatment options, including breast-conserving surgery—usually combined with radiotherapy—and mastectomy, are associated with notable physical, psychological, and socioeconomic burdens, fueling persistent concerns regarding optimal treatment strategies and the need to balance

* Corresponding author.
E-mail address: luca.nicosia@ieo.it (L. Nicosia).

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oncological safety with quality of life [9,10]. Taken together, these observations underscore the heterogeneous nature of DCIS and the persistent uncertainty surrounding its biological behaviour and clinical trajectory. Increasing attention is being paid to personalised management approaches for DCIS based on molecular profiling and imaging evaluation to tailor interventions to individual risk profiles [11]. Active surveillance protocols for selected low-risk DCIS cases have gained traction and are currently being investigated in clinical trials to reduce treatment-related morbidity without compromising oncological outcomes [12]. However, one of the most pressing limitations of de-escalation approaches is the non-negligible rate of diagnostic underestimation—cases initially diagnosed as pure DCIS on core biopsy but subsequently upstaged to invasive BC upon surgical excision [13,14]. This is a critical consideration when selecting patients for conservative management, as a higher risk of underestimation should be carefully discussed within shared decision-making processes when considering active surveillance strategies, to minimize the risk of undertreatment. Radiological assessment plays a pivotal role in this setting, as it enables the identification of imaging features suggestive of higher-risk disease, supports accurate staging, and informs decision-making [15]. Several studies have highlighted factors associated with a lower likelihood of underestimation, including the use of vacuum-assisted biopsy (which offers greater tissue sampling and diagnostic accuracy than conventional core needle biopsy), smaller lesion size, radiologically apparent macroscopic lesion removal at biopsy, and patient age [15,16]. However, less is known about the different risks associated with the main radiological manifestations of DCIS: the calcified and non-calcified forms [17]. Calcified DCIS, representing most screen-detected cases, is readily identified on mammography as fine linear or branching microcalcifications, often in a clustered or segmental distribution, reflecting intraductal epithelial necrosis [18–20]. In contrast, non-calcified DCIS is less common and diagnostically more elusive. It lacks mammographically visible microcalcifications and may instead manifest as subtle abnormalities, such as asymmetric densities or architectural distortion [21], often sampled by ultrasound guidance. Although less frequent, non-calcified DCIS deserves careful consideration, given the overall prevalence of in situ carcinoma and its potential for diagnostic misclassification [22]. A better understanding of potential differences in upstaging risk between calcified and non-calcified DCIS may have important clinical implications, particularly in the context of risk stratification and individualized management. Accordingly, the aim of this study was to investigate whether radiological presentation (calcified vs. non-calcified DCIS) is associated with differences in histopathological upstaging, after matching for the main clinicopathological and biopsy-related factors known to influence diagnostic underestimation [23].

Materials and methods

This retrospective, monocentric study was approved by the Ethics Committee of the European Institute of Oncology (approval number UID 598; approval date: May 8, 2024). Given the retrospective design of the study, the requirement for individual informed consent was waived by the Institutional Review Board in accordance with institutional and ethical guidelines. We selected all patients diagnosed with breast DCIS without radiological evidence of microcalcifications (non-calcified DCIS) between 2000 and 2023. In all these cases, the lesions were not visible on mammography and were sampled using ultrasound-guided vacuum-assisted breast biopsy (US-VABB), which is the standard diagnostic approach at our institution for small (<15 mm), sonographically visible lesions with no mammographic correlate and/or poorly defined margins. Lesion size was defined based on pre-biopsy imaging assessment and was not applied as a strict inclusion threshold; therefore, larger lesions were also included when considered suitable for vacuum-assisted biopsy. A corresponding cohort of patients with calcified DCIS, identified by the presence of mammographic microcalcifications and sampled using stereotactic VABB, was subsequently selected. To ensure a clear comparison, we excluded any cases with mixed radiological features, such as microcalcifications associated with a mass lesion. For each non-calcified case, one calcified DCIS case was selected as a matched control in a 1:1 ratio. Matching was based on age at biopsy (±5 years), histological grade (low, intermediate, or high), and radiologically apparent macroscopic lesion removal at biopsy. Lesion size was defined as the maximum lesion diameter measured on pre-biopsy imaging (ultrasound or mammography, according to radiological presentation). Complete macroscopic removal was defined as the absence of any residual visible lesion on immediate post-biopsy imaging, as assessed by the performing radiologist at the end of the vacuum-assisted biopsy procedure and documented in the procedural report. This parameter was used as a pragmatic surrogate of sampling adequacy in routine vacuum-assisted biopsy practice. All the variables were selected based on their established role in influencing diagnostic underestimation following percutaneous biopsy and were therefore considered relevant confounders of the association under investigation [14–16]. Radiological features were derived from contemporaneous clinical reports issued by board-certified breast radiologists.

Inclusion criteria:

- Histological diagnosis of DCIS (with or without microcalcifications) obtained via VABB;
- Surgical excision performed at our institution following biopsy.

Exclusion criteria:

- Diagnosis other than pure DCIS (e.g., microinvasive or invasive carcinoma);
- Surgery performed at a different facility;
- Mixed (both calcified and non-calcified) radiological presentations;
- Biopsy performed with techniques other than VABB;
- Inability to find a matched calcified case for a given non-calcified one.

The objective of the study was to evaluate the impact of radiological presentation (calcified vs. non-calcified) on the risk of histological upstaging to invasive carcinoma in patients with DCIS. Pathological data were obtained from original histopathological reports generated by board-certified pathologists with dedicated expertise in breast pathology [24]. No centralized retrospective image or pathology review was performed.

Statistical analysis

Descriptive statistics were reported for demographic and tumour characteristics, both overall and stratified by radiological presentation (calcified vs. non-calcified DCIS). For the comparison between matched groups, the variables not included in the matching algorithm were analysed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Univariable and multivariable logistic regression analyses were performed to investigate associations between upstaging and potential predictors, including calcification status, age at biopsy, lesion size, and histologic grade at biopsy. Variables were selected a priori based on clinical relevance. *Matching was applied at the design stage to improve baseline comparability; statistical analyses treated the two groups as independent.*

All p-values were two-tailed, and a value of < 0.05 was considered statistically significant.

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 119 patients with ultrasound-guided VABB-diagnosed DCIS and 2,306 patients with stereotactic biopsy-diagnosed DCIS were initially considered. After excluding 21 and 247 cases, respectively, due to the presence of mixed forms (masses with calcifications), 98 non-calcified and 2,059 calcified patients were available for matching. One matched calcified control was selected for each non-calcified case, resulting in a final study cohort of 196 patients (98 in each group). The two groups were matched based on age at biopsy (±5 years), histological grade at biopsy, and radiologically apparent macroscopic lesion removal.

The study flow diagram is shown in Fig. 1.

The median age at biopsy was 52 years (range 34–86) in both groups. Most cases were intermediate (52%) and low-grade DCIS (43%). Eighty-eight patients (45%) had complete removal of the lesion at biopsy. Lesion size did not differ significantly between non-calcified and calcified DCIS (median 12.5 mm vs. 10 mm, respectively; $p = 0.61$). Table 1 summarizes the full demographic and pathological profile.

Overall, 27 out of 196 cases (13.8%) were upstaged to invasive breast cancer at surgery. The upstaging rate was significantly higher among patients with non-calcified DCIS compared to those with calcified lesions (19.4% vs. 8.2%; $p = 0.013$). This difference remained significant in both univariable and multivariable logistic regression analyses. Specifically, calcified DCIS was associated with a lower risk of upstaging (adjusted OR: 0.31; 95% CI: 0.12–0.78; $p = 0.013$).

Lesion size was also independently associated with underestimation: each 5-mm increase conferred 21% higher odds of upstaging (OR per 5 mm: 1.21; 95% CI: 1.06–1.38; $p = 0.005$). Age at biopsy was not significantly associated with upstaging risk (OR per 5-year increase: 1.01; $p = 0.91$). These findings are summarized in Table 2.

Table 1
Patients' demographic and tumour characteristics, overall and stratified by radiological presentation (calcified vs non-calcified) (N=196).

Variable	Level	Total (N=196)	Non-calcified DCIS (N=98)	Calcified DCIS (N=98)	P-value
Age at biopsy (years), median (min-max)		52 (34-86)	52 (34-86)	52 (34-85)	*
Histology at biopsy, N (%)	DCIS G1	84 (42.9)	42 (42.9)	42 (42.9)	*
	DCIS G2	102 (52.0)	51 (52.0)	51 (52.0)	
	DCIS G3	10 (5.1)	5 (5.1)	5 (5.1)	
Complete removal (biopsy), N (%)	No	108 (55.1)	54 (55.1)	54 (55.1)	*
	Yes	88 (44.9)	44 (44.9)	44 (44.9)	
Lesion size (mm), median (min-max) (pre biopsy)		12 (3-80)	12.5 (4-60)	10 (3-80)	0.61
Surgical outcome, N (%)	DCIS G1	40 (20.4)	25 (25.5)	15 (15.3)	**0.013**
	DCIS G2	82 (41.8)	39 (39.8)	43 (43.9)	
	DCIS G3	17 (8.7)	7 (7.1)	10 (10.2)	
	DCIS and lobular carcinoma	9 (4.6)	2 (2.0)	7 (7.1)	
	Invasive ductal carcinoma	27 (13.8)	19 (19.4)	8 (8.2)	
	No residual tumor	21 (10.7)	6 (6.1)	15 (15.3)	

* Matching variables
Statistically significant values are shown in bold ($p < 0.05$)

Discussion

This study investigated whether radiological presentation is associated with differences in the risk of histological upstaging to invasive breast cancer in patients with ductal carcinoma in situ (DCIS). Within a

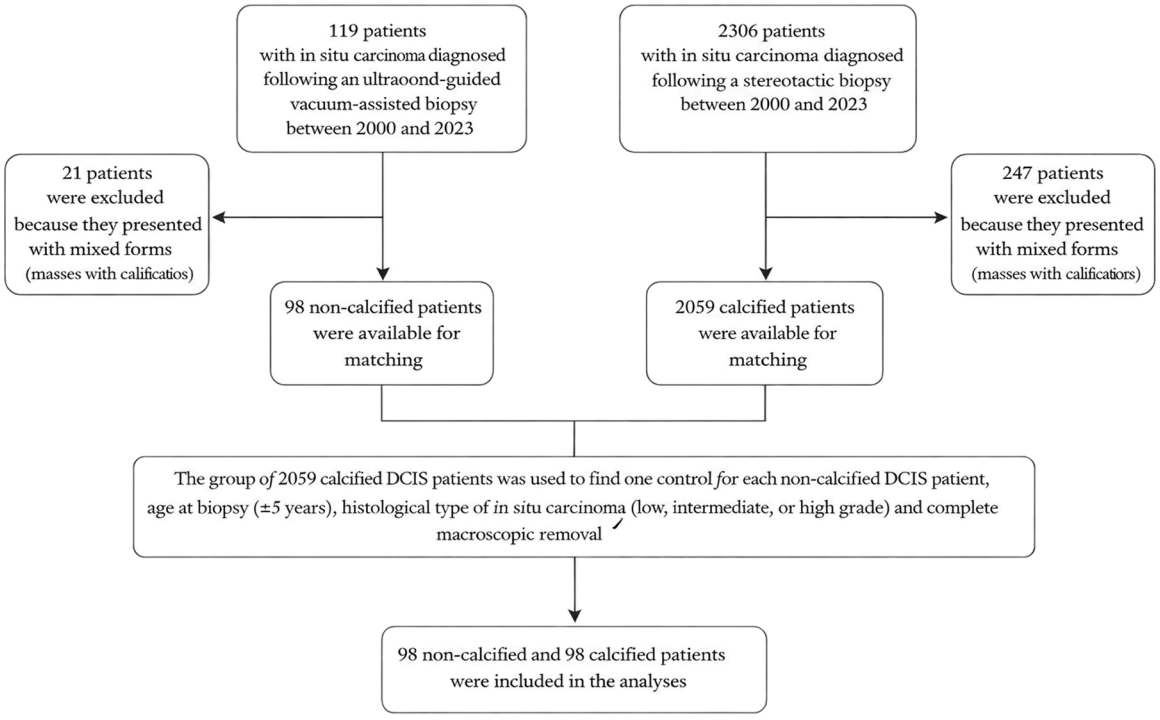

Fig. 1. Flowchart illustrating the patient selection process. The diagram shows the initial cohorts based on biopsy modality (ultrasound-guided vs stereotactic), the exclusion criteria applied (e.g., mixed lesions, lack of imaging or follow-up), and the final matched sample of 196 patients (98 calcified, 98 non-calcified DCIS).

Table 2
Association of biopsy-related and radiological factors with histological upstaging to invasive carcinoma.

Variable	Level	Upstage / Tot (%)	Univariable analysis			Multivariable analysis		
			OR	95% CI	P-value	OR	95% CI	P-value
Overall	-	27 / 196 (14%)	-	-	-	-	-	-
Histology at biopsy	DCIS G1	11 / 84 (13%)	Ref.	-	-	Ref.	-	-
	DCIS G2	15 / 102 (15%)	1.14	0.50-2.65	0.75	1.20	0.50-2.91	0.68
	DCIS G3	1 / 10 (10%)	0.74	0.09-6.40	0.78	0.83	0.09-7.59	0.86
Age at biopsy	+5 years		0.99	0.83-1.19	0.94	1.01	0.84-1.21	0.91
Lesion size	+5 mm		1.17	1.03-1.33	0.013	1.21	1.06-1.38	**0.005**
Calcification status	Non-calcified DCIS	19 / 98 (19%)	Ref.	-	-	Ref.	-	-
	Calcified DCIS	8 / 98 (8%)	0.37	0.15-0.89	0.027	0.31	0.12-0.78	**0.013**

Statistically significant values are shown in bold ($p < 0.05$)

rigorously matched cohort, we found that non-calcified DCIS was associated with a significantly higher risk of invasive upstaging compared with calcified disease, despite controlling for the main clinicopathological and biopsy-related factors known to influence diagnostic underestimation. Although non-calcified DCIS accounts for only about 10% of all DCIS diagnoses [1], its clinical relevance has been increasing in the context of widespread screening and the growing interest in treatment de-escalation strategies for selected low-risk cases [1–9]. In this setting, the present study adds to the existing literature by providing a direct comparison between calcified and non-calcified DCIS within a rigorously matched cohort, specifically designed to minimize confounding related to biopsy technique and baseline lesion characteristics (Table 3).

We controlled for key variables known to affect the risk of underestimation, namely, patient age, lesion size, histologic grade, biopsy technique, and completeness of macroscopic removal [15,16]. This methodological strength allowed for a more isolated assessment of the impact of radiological presentation on the risk of invasive upstaging in DCIS [25]. Another strength of this work is the substantial inclusion of cases diagnosed via ultrasound-guided vacuum-assisted breast biopsy (US-VABB), particularly in the non-calcified group. Most existing literature on non-calcified DCIS is based on core needle biopsy (CNB), a technique associated with a higher risk of diagnostic underestimation in this setting [26,27]. In contrast, VABB enables retrieval of larger tissue volumes, enhancing the likelihood of capturing representative areas of the lesion and significantly reducing the risk of underestimation compared to CNB [15,16]. In some cases, VABB may even achieve complete macroscopic removal during sampling, further improving diagnostic reliability [16].

This distinction may be of interest in the broader context of ongoing active surveillance trials, such as COMET, LORIS, LORD, and LORETTA, which are exploring the safety of non-operative management strategies in selected patients with low-risk DCIS [28–31]. Although still investigational, these protocols underscore the importance of accurate preoperative diagnosis to minimize the risk of underestimation. In this regard, the use of vacuum-assisted biopsy techniques, especially for radiologically non-calcified DCIS, could represent one of several imaging and procedural factors that may warrant consideration in future studies [28–31]. Radiological factors, such as lesion morphology and biopsy modality, are often overlooked in the inclusion criteria for these trials, yet may be critical for candidate selection and reducing underestimation risk [15,16]. In our study, non-calcified DCIS diagnosed via ultrasound-guided VABB was associated with a significantly higher rate of invasive upstaging compared with calcified DCIS diagnosed by stereotactic VABB (19% vs. 8%). This finding aligns with previous reports indicating that the absence of microcalcifications may hinder lesion delineation, increasing diagnostic uncertainty [32]. Furthermore, ultrasound-guided biopsy procedures may be more operator-dependent, potentially affecting sampling quality [33]. From a clinical standpoint, these data suggest a potential role for additional imaging—such as contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced mammography (CEM)—after biopsy of non-calcified DCIS in ruling out occult invasive disease [34]. A representative case of non-calcified DCIS is illustrated in Fig. 2. Taken together, our findings emphasize the importance of a multidisciplinary approach to DCIS management. Radiological features, particularly the presence or absence of microcalcifications, should not be regarded as mere diagnostic observations, but as meaningful components of risk stratification and treatment decision-making. Their systematic inclusion may enhance the safety of non-surgical strategies and enable a more personalized therapeutic approach (Fig. 3).

This study has several limitations. Its retrospective, single-center design may limit generalizability, and the long inclusion period (2000–2023) introduces potential heterogeneity related to evolving imaging technologies and clinical practice, despite the use of consistent biopsy techniques. Radiological classification was based on contemporaneous clinical reports without centralized image re-reading or blinded review, and some degree of misclassification cannot be excluded. The assessment of complete macroscopic removal relied on post-biopsy imaging and procedural reports and may be subject to operator-dependent variability. Although the matching strategy was designed to control for the main predictors of diagnostic underestimation, residual confounding cannot be entirely ruled out. The number of upstaging events was limited by case availability, which may affect the precision of the multivariable analysis. Finally, the extensive use of ultrasound-guided vacuum-assisted biopsy, particularly in the non-calcified cohort, may

Table 3
Multivariable models evaluate the association of age at biopsy, lesion size, and radiological presentation with Ki-67, grading, and HER2 status.

Variable	Level	Tumor characteristic								
		Ki-67>20%			Grading≥2			HER2 status Positive		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age at biopsy	+5 years	0.94	0.81-1.10	0.45	0.88	0.76-1.01	0.071	1.10	0.92-1.32	0.29
Lesion size	+5 mm	1.09	0.97-1.23	0.13	1.06	0.93-1.22	0.38	1.05	0.91-1.22	0.47
Calcification status	Non-calcified DCIS	Ref.	-	-	Ref.	-	-	Ref.	-	-
	Calcified DCIS	0.95	0.47-1.89	0.88	2.99	1.46-6.09	0.003	0.98	0.41-2.33	0.97

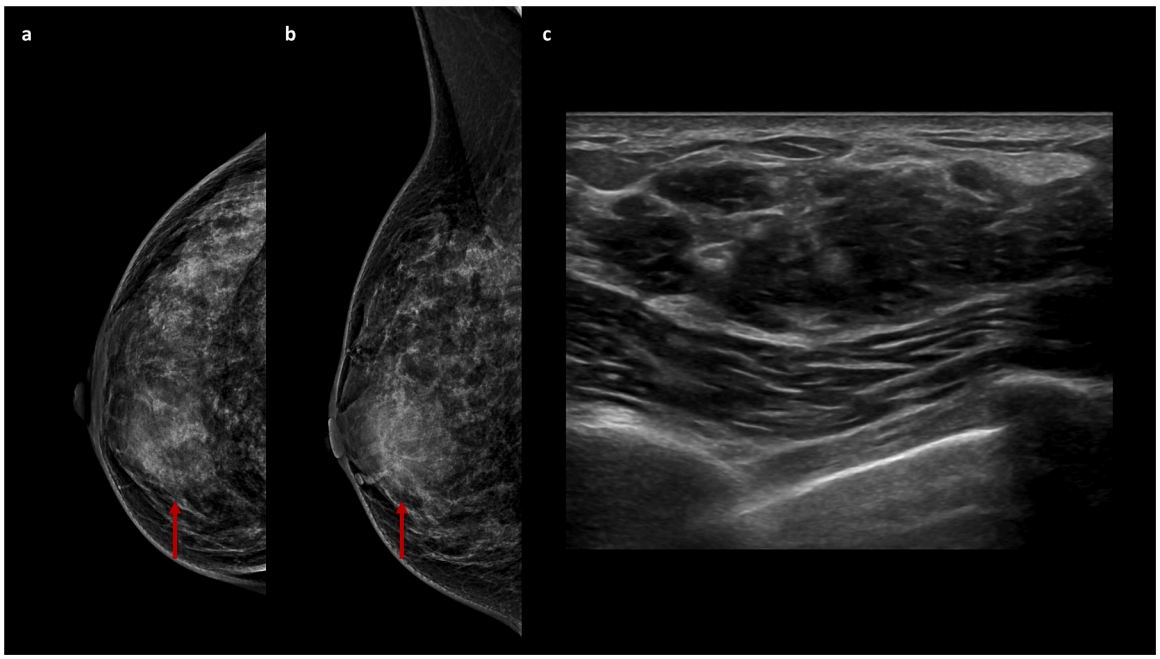

Fig. 2. Representative case of non-calcified DCIS. (a) Cranio-caudal and (b) medio-lateral oblique mammographic views of the right breast show a subtle fuzzy opacity in the retro-parareolar region (red arrows). (c) Corresponding ultrasound image reveals an ill-defined, inhomogeneous hypoechoic area consistent with the mammographic finding.

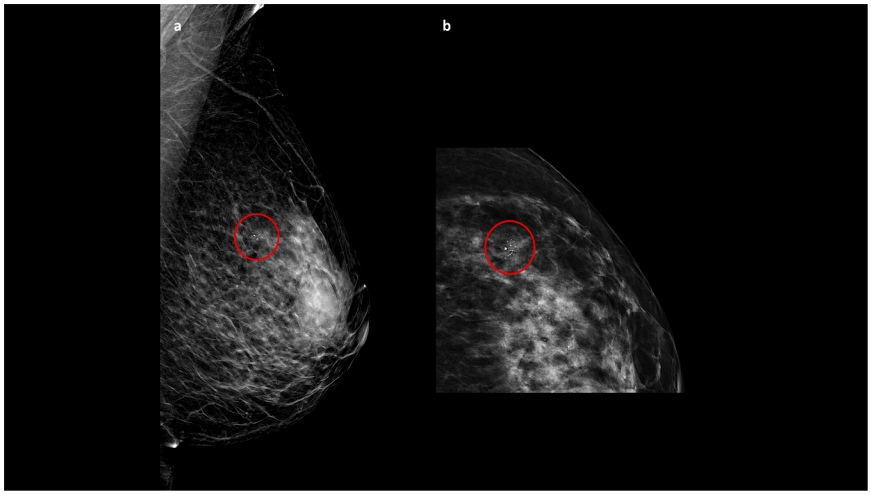

Fig. 3. Representative case of calcified DCIS. (a) Medio-lateral oblique mammographic view of the left breast shows a cluster of fine pleomorphic microcalcifications in the upper-outer quadrant (red ring). (b) The focused magnification highlights the suspicious morphology and distribution of the calcifications.

limit extrapolation of the findings to settings where conventional core needle biopsy is more commonly used. Despite these limitations, the results should be interpreted as exploratory and warrant validation in larger, prospective, multicenter studies. Nonetheless, this study provides valuable insights into the role of radiological presentation in the diagnostic assessment of DCIS.

Conclusion

Our findings indicate that radiological presentation of DCIS provides clinically meaningful information for risk stratification. In particular, the absence of mammographic microcalcifications—more frequently associated with diagnostic underestimation—may help identify cases in which additional preoperative assessment could be warranted to exclude occult invasive disease.

Although active surveillance is not currently part of standard clinical practice, future risk-adapted management strategies may consider radiological phenotype, alongside other established factors, when exploring de-escalation approaches. Overall, these results underscore the potential value of imaging characteristics in supporting a more individualized and multidisciplinary approach to DCIS management.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used *ChatGPT* (GPT-

5.2, OpenAI) to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Ethics approval and consent to participate

The local ethics committee approved this retrospective study and waived the requirement for specific informed consent (approval number UID 4622; approval date: May 8, 2024).

Consent for publication

Ethics committee approval for the retrospective study was granted (approval number UID 598; approval date: May 8, 2024) after verification of the institutional consent proposed to patients at our institution (general consent to scientific research). All data were anonymized. Figures do not contain sensitive data and cannot be traced back to individual patients.

CRediT authorship contribution statement

Luca Nicosia: Conceptualization. **Luciano Mariano:** Resources. **Carmen Mallardi:** Investigation. **Filippo Pesapane:** Resources. **Lorenza Meneghetti:** Resources. **Francesca Abbate:** Resources. **Samuele Frassoni:** Software. **Vincenzo Bagnardi:** Supervision, Software. **Cristian Gialain:** Data curation. **Giovanni Corso:** Supervision. **Nicola Fusco:** Supervision. **Enrico Cassano:** Supervision.

Declaration 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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Data availability

The data presented in this study (raw data) are available upon request from the corresponding author. Due to privacy considerations and GDPR compliance, the data are not publicly available.

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