MedCrave
Step into the World of Research
Journal of Cancer Prevention & Current Research

Case Report

Open Access
CrossMark

Heterogeneity of extensive invasive lobular carcinoma. part II: combination of the classic extralobular diffuse subtype with intralobular colonies of invasive lobular carcinoma

Abstract

Background: The classic, diffuse invasive lobular carcinoma (ILC) consists of malignant cells arranged in single files spreading throughout much of the extralobular breast mesenchyme and separated by layers of newly formed fibrous connective tissue. An unappreciated variant of ILC consists of a similar microscopic appearance but with the malignant cells mostly restricted to the intralobular mesenchyme, surrounding the terminal ducts and acini, which have histopathologically normal breast lobular epithelia. These intralobular ILC foci form colonies reaching sizes of one or more centimetres. We report here an extensive (75x43 mm) tumour diagnosed as ILC and consisting predominantly of these malignant intralobular colonies, and compare the long-term follow-up of 312 consecutive intralobular and extralobular cases sized ≥20 mm.

Case presentation: A 72-year-old woman presented with a self-detected extensive thickening in the retroareolar and central portion of her right breast, associated with nipple-areola retraction. Three consecutive mammographic examinations are presented; the first at age 69, 30 months before diagnosis (normal), the second 23 months later, and the third seven months later, at age 72, when she presented with clinical symptoms. The histopathologic diagnosis was a 75x43 mm-sized ILC tumour consisting of many colonies with the above-described concentric arrangement of malignant cells situated within the intralobular mesenchyme. There have been no signs of recurrence at her annual follow-up examinations, the most recent being eleven years and two months after her mastectomy.

Results: The 15-year survival of the intralobular cases was 92 % versus a significantly poorer 69% survival of the extralobular cases.

Conclusions: There are two distinct subtypes of classic ILC, one of which is the extensive, classic, diffusely invasive lobular carcinoma and another, which is the hitherto unappreciated ILC variant, where the malignancy is mostly confined to the intralobular mesenchyme of the terminal ductal lobular units (TDLUs). The overall extent of these intralobular colonies is commonly restricted to 1-19 mm. The malignant cells within each affected TDLU surround the terminal ducts and acini containing normal luminal epithelial cells. These two breast malignancy subtypes have vastly different long-term outcomes and divergent clinical, imaging, histopathologic, and long-term outcome characteristics. This case report describes an extensive malignancy in which the classic, extralobular, diffuse subtype combines with colonies of invasive lobular carcinoma, and has a predominance of the intralobular subtype.

Key words: Breast cancer, invasive lobular carcinoma, imaging biomarkers, breast cancer of mesenchymal origin

Volume 17 Issue 3 - 2026

László Tabár,[1] Peter B Dean,[2] Miklós Tarján,[3] Wendy Yi-Ying Wu,[4] Hsiu-HsiChen,[5] Amy Ming-Fang Yen[6]

[1]Department of Mammography, Falun Central Hospital, Sweden
[2]Department of Diagnostic Radiology, Faculty of Medicine, University of Turku, Finland
[3]Department of Clinical Pathology and Cytology, Falun Central Hospital, Sweden
[4]Department of Radiation Sciences, Oncology, Umeå University, Sweden
[5]National Taiwan University, Taipei, Taiwan
[6]School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taiwan

Correspondence: László Tabár, Department of Mammography, Falun Central Hospital,791 82 Falun, Sweden, Falun, Sweden

Received: April 23, 2026 | **Published:** May 18, 2026

List of abbreviations: BCMO, breast cancer of mesenchymal stem cell origin; ILC, invasive lobular carcinoma; TDLU, terminal ductal lobular unit

Introduction

The classic diffuse, invasive lobular carcinoma (ILC) causes an extensive, firm thickening at clinical breast examination.[1] Its mammographic imaging biomarker is non-calcified architectural distortion.[2] The consistently high fatality rate has not been reduced by recent therapeutic developments. Current therapeutic regimens have difficulty in controlling this malignancy.[3] The term ILC is used to describe not only this subtype but also a clinically and histopathologically distinct subtype, a screen-detected, non-palpable stellate or circular tumour, usually smaller than 2 centimetres in size, and having a considerably better long-term patient outcome than the classic, diffuse form.[1,2] The pathologist András Vörös brought our attention to this variant of ILC where the malignancy was present within the mesenchyme of the TDLU.[4] He demonstrated that the "invasive lobular carcinoma" cells within the TDLU were E-cadherin negative and had cellular features clearly different from the normal epithelial cells lining the terminal duct(s) and acini, which were E-cadherin positive. This insight has several implications for diagnosticians and therapists alike. Searching for an alternative site of origin of the cancer cells, we excluded the adipose tissue within the TDLU, leaving the intralobular mesenchyme as the only remaining alternative. Our cell culture study on diffusely invasive lobular carcinoma had previously demonstrated the capability of the hybrid

stem cells of the mesenchyme to undergo mesenchymal-epithelial transition,[5] so we proposed that the intralobular mesenchymal hybrid stem cells could also undergo a similar mesenchymal epithelial transition confined to the terminal lobular units and suggested the term intralobular breast cancer of mesenchymal stem cell origin.[4]

Case description

A 69-year-old asymptomatic woman attended routine mammography screening and her mammograms (Figure 1) were diagnosed as normal. At routine screening 23 months later, when she was still asymptomatic, her mammograms (Figure 2) were again read as normal. Retrospectively evaluated, the first examination was indeed normal, but the following examination showed subtle but extensive architectural distortion in the right upper-outer quadrant. Only seven months later, at age 72 during the interscreening interval, she noted right nipple-areola retraction and extensive thickening in the upper-outer quadrant of her right breast. Clinical breast examination confirmed these findings. Neither nipple discharge nor pathologic axillary lymph nodes were observed. Corresponding to the clinical examination findings, mammography (Figure 3) and microfocus magnification mammography (Figure 4) showed nipple-areola thickening and retraction associated with architectural distortion measuring 7x4 cm, having no associated microcalcifications. Retrospective application of an artificial intelligence algorithm (Figure 5) pointed out a pathologic lesion already in the second examination. Automated (Figure 6) and hand-held breast ultrasound (Figure 7) as well as breast MRI (Figure 8) clearly demonstrated the presence and extent of the disease. Microscopic examination of the ultrasound-guided 14G core biopsy specimen diagnosed classic invasive lobular carcinoma. Mastectomy was performed and mastectomy slice specimen radiographs were compared with large format thin and thick (subgross, 3D) section histopathology examination (Figure 9), which revealed a 75x34 mm combination of the extralobular and intralobular BCMOs, with the predominance of the intralobular BCMO colonies. Immunohistochemical biomarkers: ER/PR positive, Ki67 15%, E-cadherin negative. The ER positive cancer cells encircled a normal terminal duct and acini (Figure 10). Lymph vessel invasion was present. No metastases were found in two surgically removed axillary lymph nodes (pN 0/2). The normal epithelial cells lining a subsegmental duct, the terminal duct and the acini were positive at E-cadherin staining, while the surrounding cancer cells were E-cadherin negative.

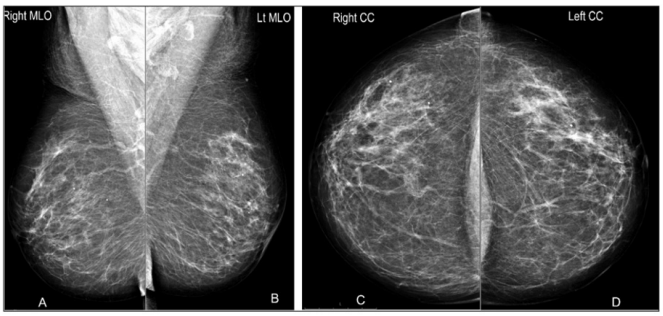


Figure 1 Normal prior medio-lateral (A,B) and craniocaudal (C,D) screening mammograms at age 69.

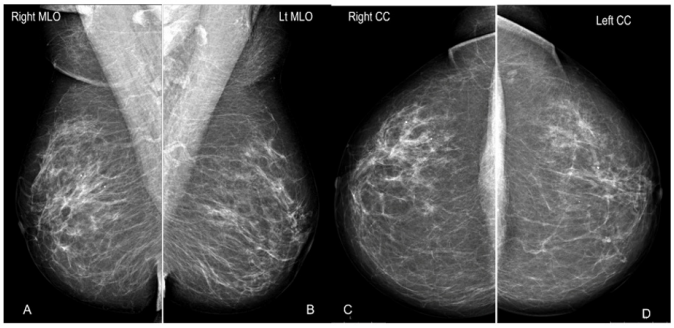


Figure 2 Medio-lateral (A,B) and craniocaudal (C,D) screening mammograms twenty-three months later, interpreted as normal.

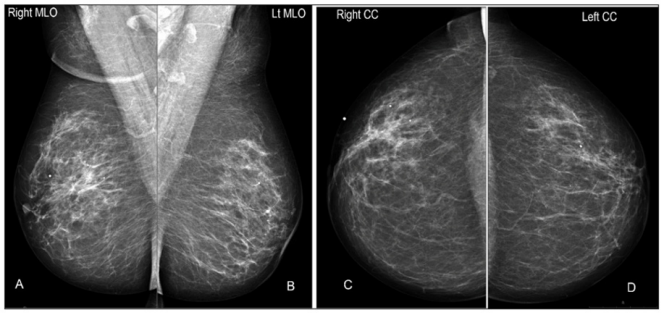


Figure 3 Medio-lateral (A,B) and craniocaudal (C,D) clinical mammograms seven months later, at age 72. The palpable thickening in the right upper-outer quadrant, indicated by a lead pellet, corresponds to extensive but subtle architectural distortion.

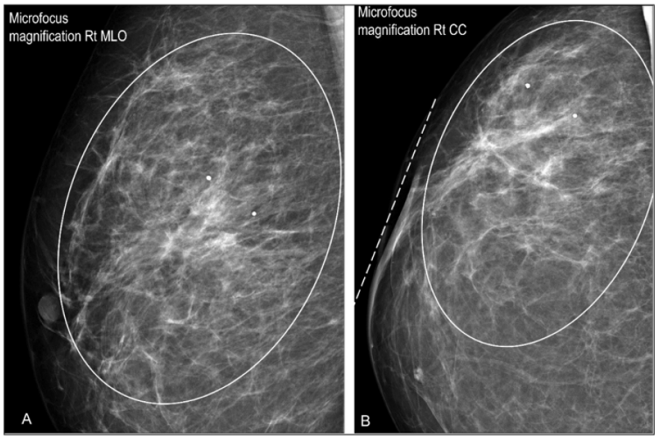


Figure 4 Medio-lateral (A) and cranio-caudal (B) microfocus magnification mammograms of the extensive architectural distortion causing skin and nipple-areola retraction and thickening.

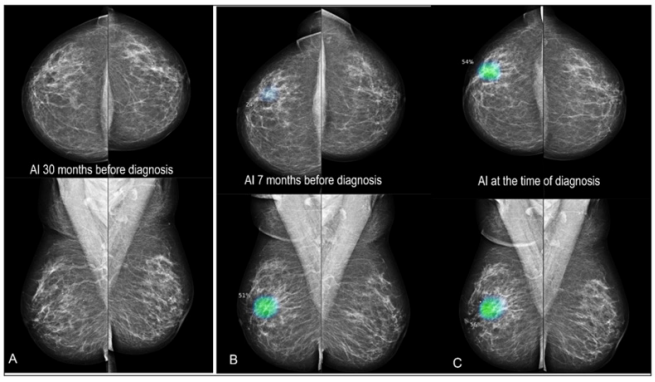


Figure 5 A retrospectively applied artificial intelligence algorithm pointed out the abnormality already at the second examination.

Citation: Tabár L, Dean PB, Tarján M, et al. Heterogeneity of extensive invasive lobular carcinoma. part II: combination of the classic extralobular diffuse subtype with intralobular colonies of invasive lobular carcinoma. *J Cancer Prev Curr Res.* 2026;17(3):66–70. DOI: 10.15406/jcpcr.2026.17.00609

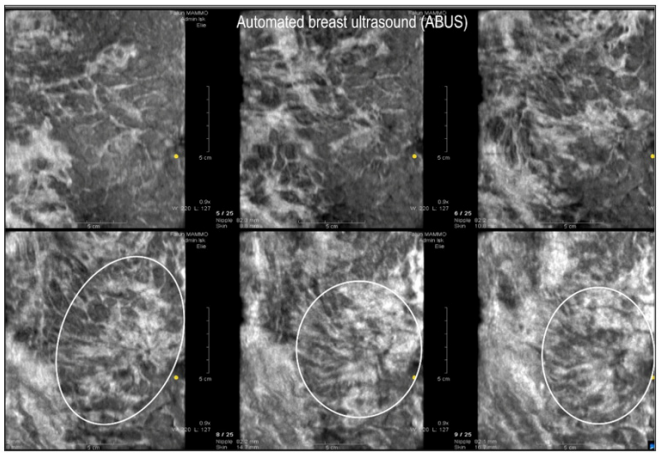


Figure 6 Series of automated breast ultrasound image slices show architectural distortion and a tissue defect characteristic of an extensive malignant process.

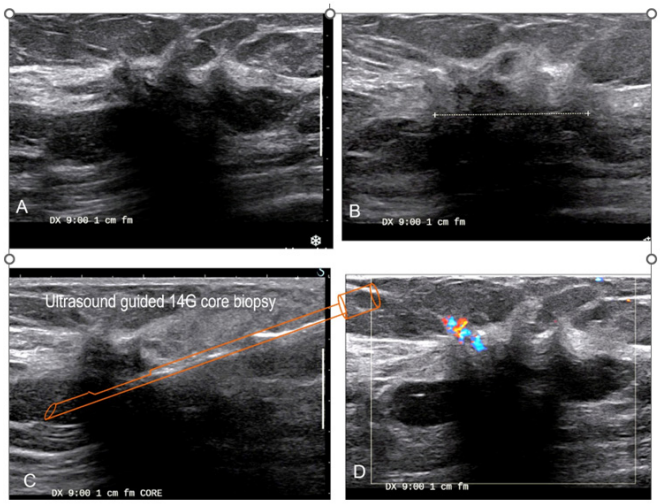


Figure 7 Hand-held ultrasound (A,B), including Doppler (D) and ultrasound guided 14G core biopsy (C). The predominance of fibrous mesenchyme in the diffusely infiltrating breast malignancy enables imaging with greater sensitivity by ultrasound than by mammography. The thin sheets or veils of tissue are poorly penetrated by ultrasound but are relatively easily penetrated by X-rays.

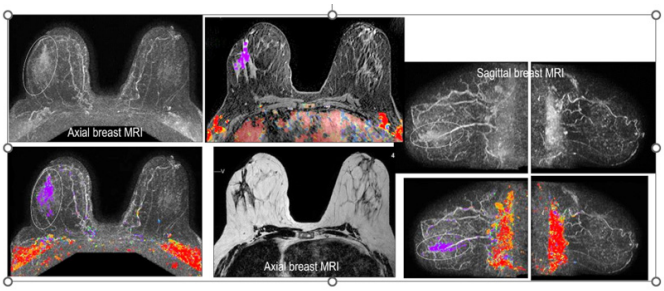
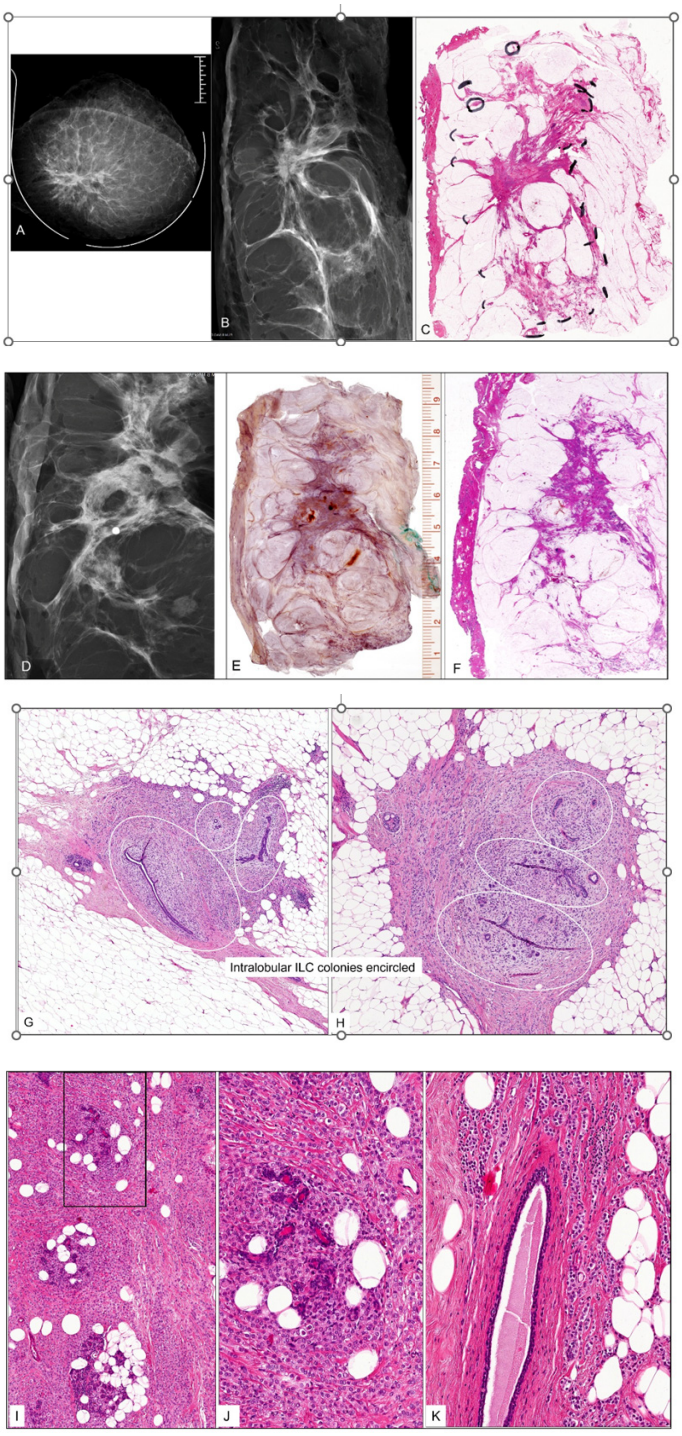


Figure 8 Breast MRI in axial and sagittal views demonstrates much of the extent of the disease.



Citation: Tabár L, Dean PB, Tarján M, et al. Heterogeneity of extensive invasive lobular carcinoma. part II: combination of the classic extralobular diffuse subtype with intralobular colonies of invasive lobular carcinoma. *J Cancer Prev Curr Res.* 2026;17(3):66–70. DOI: 10.15406/jcpcr.2026.17.00609

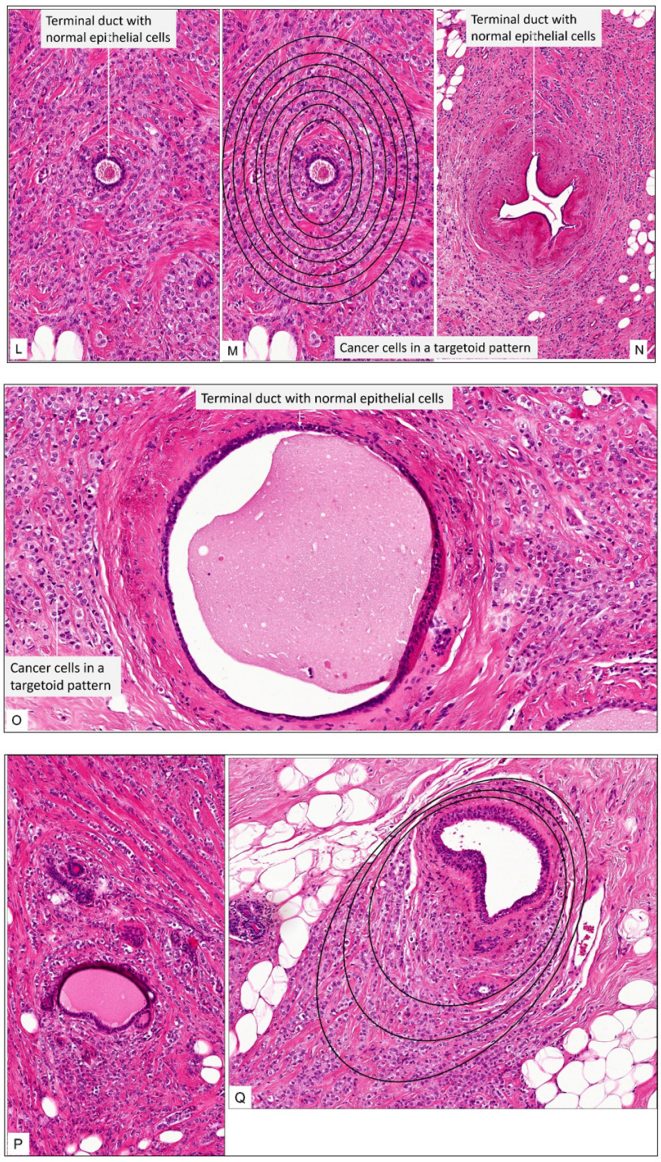


Figure 9 Mastectomy specimen radiograph (A). The mastectomy specimen slice radiographs (B,D) are correlated with the corresponding large format thin (C,F) and thick (E) section histopathology images. Low (G,H,I,N), intermediate (J,K) and high-power histopathology images (L,M,O-Q) illustrate the normal epithelia of the terminal ducts and acini surrounded by the cancer cells in targetoid pattern.

Follow-up: During eleven years of annual follow-up, the patient remained well with no recurrence of the disease.

Divergent long-term outcome of the intralobular versus the extralobular BCMO cases

We have previously described an unappreciated "classic invasive lobular carcinoma" confined to the terminal ductal lobular unit(s) and suggested the term: intralobular breast cancer of mesenchymal stem cell origin.[3,4] The majority of these intralobular BCMO cases measures 1-19 mm in size. This case is representative of the extensive, several centimetre sized BCMO cases where a palpable tumour contains multiple colonies consisting of small, intralobular BCMO foci. We have compared the long-term survival of extensive BCMO cases composed primarily of intralobular colonies with predominantly diffuse, invasive extralobular BCMOs. A total of 315 BCMO cases ≥20 mm were diagnosed in Dalarna County, Sweden from January 2008 through June 2022 with follow-up through October 2025. There were 64 fatalities among 275 women with extralobular cancer and 3 fatalities among 40 women having intralobular cancer colonies. Routine use of the large section (8x10 cm) histopathology technique facilitated correlation with multimodality imaging findings, enabling the distinction between these two disease subgroups. The 69% 15-year survival of extralobular BCMO cases was significantly poorer than the 92% 15-year survival of the intralobular BCMO cases (Figure 11).

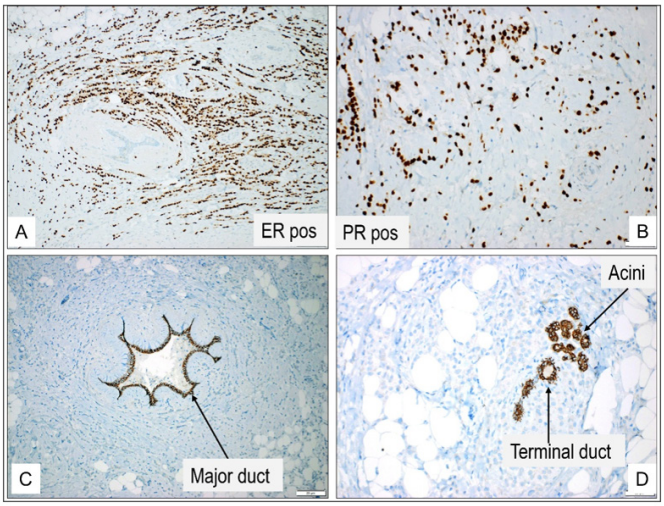


Figure 10 The estrogen positive cancer cells encircle the normal terminal duct (A). The normal epithelial cells in a subsegmental duct (C), and in a terminal duct and acini (D) stain positively using E-cadherin while the surrounding cancer cells are E-cadherin negative. ER clone SP1 from Roche, PR clone 1E2 from Roche, E-cadherin NCH-38 from DAKO.

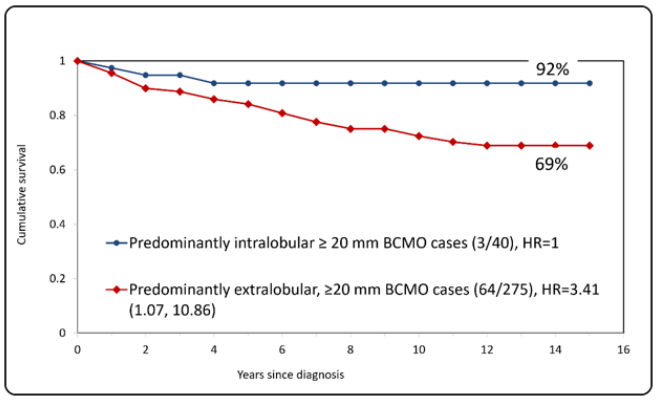


Figure 11 Fifteen-year survival of women with predominantly intralobular, ≥20 mm BCMO (92%) compared with survival of women with predominantly extralobular ≥20 mm BCMO (69%).

Discussion

The clinical, histopathologic, imaging and outcome characteristics of the classic invasive lobular carcinoma are well known.[1] Recent cell culture research performed on classic ILC provided evidence that this breast cancer subtype originates from the mesenchymal hybrid stem cells, rather than from, as its name indicates, the epithelial cells of the breast lobule.[5] The epithelial characteristics of the stem cells develop through mesenchymal-epithelial transition (MET)[6] resulting in pseudo-epithelial cells that bring to mind a "wolf in sheep's clothing."[7] We have suggested the term "breast cancer of mesenchymal stem cell origin (BCMO)" according to its site of origin in the intralobular and/or extralobular mesenchymal hybrid stem cells.[5]

Citation: Tabár L, Dean PB, Tarján M, et al. Heterogeneity of extensive invasive lobular carcinoma. part II: combination of the classic extralobular diffuse subtype with intralobular colonies of invasive lobular carcinoma. *J Cancer Prev Curr Res.* 2026;17(3):66–70. DOI: 10.15406/jcpcr.2026.17.00609

In the 5th edition of the WHO Classification of Tumours, the volume Breast Tumours states the following: "ILC originates from the functional unit of the breast, the glandular epithelial cells of the milk-producing terminal chambers (the terminal ducto-lobular unit, TDLU)".[1] Our research data challenges this assumption by concluding: "In addition to the unusual clinical, imaging, and histopathologic aspects of diffusely infiltrating breast cancer, these cell culture findings also fail to support the current assumption that this breast cancer subtype has its origin in the epithelial cells of the breast lobules."[5] "It has been argued that the occasional presence of lobular carcinoma in situ (LCIS) indicates that LCIS may be a precursor of this diffusely infiltrating carcinoma. We have found no morphologic evidence that the occasionally associated LCIS, the least aggressive of breast malignancies, could be a precursor of this highly fatal breast cancer subtype. In addition, the occasional association with LCIS does not prove causation. Its conventional name, diffusely infiltrating lobular carcinoma, carries the assumption that this subtype of breast cancer originates from the cells lining the lobules. However, this malignancy surrounds the acini containing normal lobular epithelial cells and it also surrounds the major ducts containing normal ductal epithelial cells. This prompted us to search for an alternate site of origin and carried out our cell culture study.[2]"

Further confirmation and the acceptance of a mesenchymal stem cell origin of this malignancy would be a step toward facilitating research efforts aimed at finding effective therapeutic agents for this disease subgroup that is largely resistant to current therapeutic regimens. The currently accepted assumptions of the origin of diffuse and extensive classic ILC need reconsideration, and the terminology needs revision to express a hybrid-pluripotent stem cell origin, if we are to improve the poor survival rate of this misunderstood malignancy.

The widespread use of mammography enabled detection of non-palpable breast cancers smaller than 20 mm, including many sub centimetre invasive carcinomas. The use of identical terminology for malignancies of vastly different sizes and imaging presentations, and with significant differences in long-term outcome, has been an unfortunate and misleading inconsistency for many decades.

Detailed analysis of the intralobular cancer foci clearly demonstrates the terminal ducts and acini containing normal epithelial cells that are surrounded by but apparently unaffected by the pseudo-epithelial malignant cells originating from the hybrid pluripotent stem cells of the intralobular mesenchyme. These malignant cells often form a targetoid pattern in circular, single files. The histopathologic images challenge the justification of the term "invasive lobular carcinoma" since the malignant cells could not have originated from the epithelial cells of the acini or the terminal duct, since these cells have been normal in all of our cases.

Conclusion

Mammographic detection of the diffuse, classic subtype of breast cancer of mesenchymal stem cell origin (BCMO, aka as invasive lobular carcinoma) is a considerable challenge for the breast imager due to the extensive, but subtle architectural distortion, and a lack of a solid central tumour mass and calcifications. Most of these cases are self-detected as extensive thickening and deformation of the breast rather than a distinctive tumour mass. Adjunctive imaging methods, such as hand-held ultrasound, automated breast ultrasound and breast MRI are all more sensitive than mammography and a necessary part of the imaging workup. The excessive production of fibrous connective tissue accounts for both the clinical examination and ultrasound findings. Large format histopathology examination provides adequate correlation with the imaging findings, especially when the diffuse form is associated with the solid subtype of ILC or with the intralobular subtype of BCMO. The imaging biomarker of the intralobular BCMO is either a stellate or circular/oval-shaped tumour mass, typically detected on the mammograms of asymptomatic women.

We point out a special role of the immunohistochemical biomarker, E-cadherin, which stains the normal luminal cells of the terminal ducts and acini while the surrounding cancer cells are negative at E-cadherin staining. This provides further evidence that the so-called invasive lobular carcinoma cells do not originate from the epithelial cells of the lobule, rendering the term "invasive lobular carcinoma" unjustified.

Changing the terminology to one that expresses the hybrid-pluripotent stem cell origin of these malignancies could facilitate research efforts toward finding effective therapeutic agents for this disease subgroup, because it is largely resistant to current therapeutic regimens. The currently accepted terminology and assumptions of the origin of diffuse and extensive classic ILC needs to be reconsidered if we are to improve the poor survival rate of this misunderstood malignancy.

Acknowledgements

Special thanks to Ms. Helena Hermelin, the leader of the Research Laboratory at Falun Central Hospital, for scanning the histopathology glass slides and organizing the research archive. This work has been supported by funding from the American Cancer Society through a gift from the Longaberger Company's Horizon of Hope® campaign (Project NHPDCSGBR-GBRLONG).

Conflict of interest

The authors declare that they have no competing interests.

References

1. Shin SJ, Desmedt C, Kristiansen G, et al. Invasive lobular carcinoma. In: WHO classification of tumours editorial board, breast tumours, Vol 2, fifth ed., IARC Publications, Lyon, 2019;114–118.
2. Tabár L, Dean PB, Tucker FL, et al. The challenging imaging and histopathologic features of diffusely infiltrating breast cancer. *Eur J Radiol*. 2023;161:110754.
3. Tabár L, Dean PB, Li-Sheng C, et al. Why are we failing to cure so many cases of invasive lobular breast cancer?. *J Cancer Prev Curr Res*. 2025;16(5):130–132.
4. Tabár L, Dean PB, Yen AMF, et al. The term "classic invasive lobular carcinoma" of the breast defines breast malignancies of vastly different nature. *Eur J Radiol*. 2023;168:111119.
5. Tabár L, Bozó R, Dean PB, et al. Does diffusely infiltrating lobular carcinoma of the breast arise from epithelial-mesenchymal hybrid cells?. *Int J Mol Sci*. 2023;24(13):10752.
6. Nisticò P, Bissell MJ, Radisky DC. Epithelial-mesenchymal transition: general principles and pathological relevance with special emphasis on the role of matrix metalloproteinases. *Cold Spring Harb Perspect Biol*. 2012;4(2):a011908.
7. Vernon-Jones VS. The Wolf in Sheep's Clothing. In: Æsop's Fables: A New Translation, Avenel Books, New York, 1912.