

Structural dedifferentiation of breast cancer arising within the major lactiferous ducts: imaging-histopathologic correlation in two fatal cases

Abstract

Background: Malignant neoducts arising within the major lactiferous ducts of the breast through the process of neoductogenesis undergo structural dedifferentiation, which facilitates their metastatic dissemination. The fatality of these malignancies continues to be significantly greater than that of cancers arising within the breast lobules, despite the accomplishments of early detection and the therapeutic innovations introduced over recent decades.

Precis: This report describes two fatal breast cancer cases, both of which demonstrate the documented association between structural dedifferentiation and breast cancer fatality. The 1st phase of progression of breast cancer originating within the major lactiferous ducts, ductal carcinoma *in situ* (DCIS), cannot be demonstrated with currently available imaging methods. The 2nd phase of progression, ductal adenocarcinoma of the breast (DAB), and the 3rd phase, dedifferentiated ductal adenocarcinoma of the breast (ddDAB) of this complex cancer progression are richly illustrated. An appreciation of the process of structural dedifferentiation of cancers originating within the major ducts will be key to improving the outcome of this highly fatal breast cancer subgroup.

Case description: Case 1 represents the fluid-producing diffuse breast cancers of ductal origin. Three imaging biomarkers characterize this case: extensive architectural distortion, an associated cluster of microcalcifications on the mammogram, and galactographic findings. The patient's bloody nipple discharge prompted the galactographic examination. Architectural distortion on the mammogram correlates with the fluid-filled cancerous neoducts on the galactogram. Three months after the diagnosis and initiation of treatment, the patient was diagnosed with lung metastases that had histopathologic and immunohistochemical features similar to those of the malignant neoducts (DAB) in the breast. Eight months after diagnosis the patient died from DAB and ddDAB.

Case 2 is a combination of extensive DAB and multifocal ddDAB, where the histopathologic picture of the DAB is dominated by central necrosis. Axillary lymph node metastases and a recurrence in the chest wall correspond to the 2nd phase (neoducts, DAB) and the 3rd phase (ddDAB) in the evolution of this breast malignancy originating within the major lactiferous ducts. The histopathologic image of the 3rd phase (ddDAB) dominated the picture in the liver metastases. Twelve months after initial diagnosis the patient died from DAB and ddDAB.

Conclusion: The imaging biomarkers and large section histopathology are consistent with the model of tumour development within the major lactiferous ducts. Breast cancer arising within the major ducts can be characterized by the production of necrosis and fluid in varying combinations. The imaging and histopathologic features of these two cases as well as their poor outcome are typical for DAB and ddDAB.

Key words: mammography, breast cancer neoducts, neoductogenesis, dedifferentiation of neoducts, imaging biomarkers

Volume 17 Issue 5 - 2026

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Received: September 15, 2026 | **Published:** September 22, 2026

List of abbreviations: AAB, acinar adenocarcinoma of the breast; BCMO, Breast cancer of mesenchymal stem cell origin; DCIS, Ductal carcinoma *in situ*; DAB, ductal adenocarcinoma of the breast; ddDAB, dedifferentiated DAB; EMT, Epithelial-mesenchymal-transition; H&E, haematoxylin-eosin staining; IHC, immunohistochemical; MLO, medio-lateral projection; CC, cranio-caudal projection; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor2; CK5-6, cytokeratin staining 5-6; CK14, cytokeratin staining 14; EGFR, epidermal growth factor receptor; LVI, lymph vessel invasion; TDLU, Terminal ductal lobular unit

Introduction

The two cases reported in this paper are from a comprehensive database consisting of all histologically proven breast cancer cases (n=3587), both clinically and screen-detected, diagnosed in women of all ages at the Departments of Mammography and Histopathology, Falun Central Hospital, Sweden, during the period Jan 2008-June 2022. The regional cancer registers and the national quality register provided the list of breast cancer cases. The vital status and cause of death of each patient were ascertained from the national death register through October 23, 2025.¹

Breast cancers originating from the major lactiferous ducts accounted for 570 consecutive cases in our database. The imaging biomarkers seen on the mammograms and galactograms reflect the underlying pathophysiology, either necrosis producing or fluid producing DAB or their combination. Four different types of microcalcifications (438 cases) accounted for most of the imaging biomarkers: 317 cases of fragmented casting type, 14 cases of dotted casting type, 94 cases of skipping stone-like and 13 cases of string of pearl-like calcifications. The imaging biomarkers of the fluid-producing DAB include the skipping stone-like and string of pearl-like calcifications, the galactographic findings (16 cases) and most of the non-calcified architectural distortion (116 cases). The long-term patient outcome is significantly worse in the necrosis producing DAB cases (RR=4.33 95% CI:1.73-10.84), but not the cases having architectural distortion (RR=2.51, 95% CI 0.87-7.23) compared with the fluid-producing DAB group (RR=1.0).¹

The two fatal cases presented in this report had the following imaging biomarkers: casting type calcifications, architectural distortion and galactographic findings. Large format thin section histopathology of both cases illustrates the 2nd and 3rd phases in the evolution of breast cancer originating in the major ducts. There is a striking similarity in the histologic findings and the immunohistochemical prognostic factors of the primary breast cancers and the distant metastases.

We use the official cause of death as it appears in the Death Registry to describe the outcome of the cases in this report. We have recently described the term “refined assessment of the cause of death” as follows: “Death registries do not provide information concerning the specific breast cancer subtype, although such information should be part of precision medicine because it is crucial for evaluating the success of management. For this reason, we have used a refined assessment of the cause of death to determine the subtype of the breast cancer primarily responsible for the patient’s death. This involves determining the characteristic histopathologic and immunohistochemical features of each fatal primary tumour and comparing these with the features of all available axillary node and distant metastases.”²¹

The refined diagnoses have been determined from high-resolution (0.40 µm) scans of the original histopathology slides.¹

First case

This 78-year-old woman presented with left bloody nipple discharge. The multimodality imaging approach was carried out. The mammograms showed extensive architectural distortion in the lower half of the left breast and a group of malignant type calcifications close to the chest wall (Figure 1). The galactogram outlined the fluid-filled ducts and the disorganized duct-like structures (neoducts) containing multiple filling defects (Figure 1 E,D). The findings correspond to a fluid-producing carcinoma originating in the major lactiferous ducts (DAB). The branches of the contrast-filled ducts outline a large lobe in the lower-outer quadrant. The malignant type calcifications were detected in the same region. Breast ultrasound identified a hypoechoic lesion containing small hyperechoic lesions typical of calcifications (Figure 1 J,K). Breast MRI (Figure 1 G-I) demonstrated the extent of the lesion between the nipple and the chest wall. Following preoperative ultrasound guided 14G core needle biopsy (Figure 1 L,M), mastectomy was performed. The microfocus magnification images of the mastectomy specimen slices were correlated with the large format thin section histopathology findings. Immunohistopathologic prognostic factors completed the description of the case. The histopathologic images demonstrate numerous

examples of structural dedifferentiation, transition between the 2nd and 3rd phases in the evolution of breast cancer originating in the major lactiferous ducts.

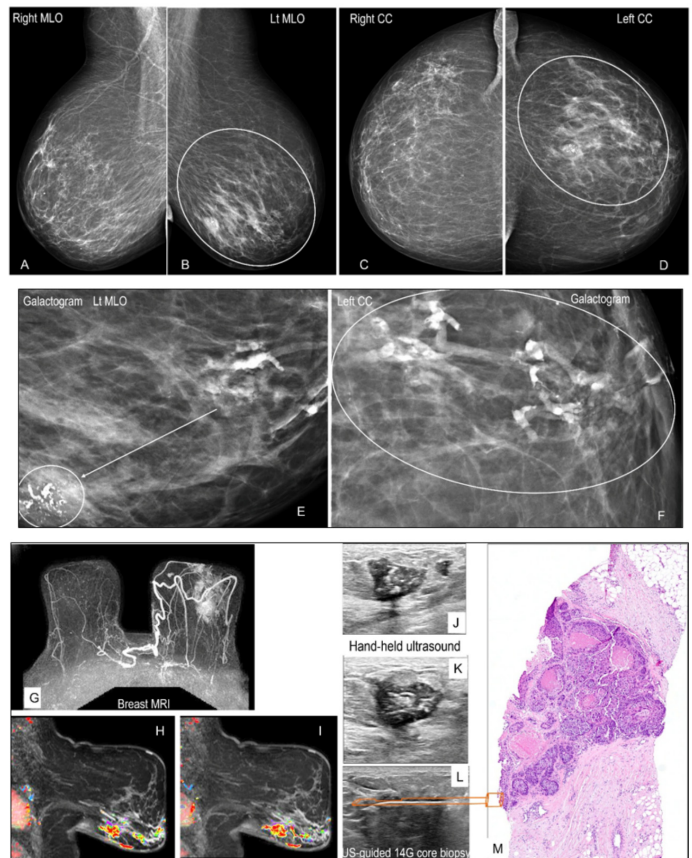


Figure 1 Medio-lateral (A,B) and cranio-caudal (C,D) mammograms. The patient had bloody nipple discharge. The extensive asymmetric density in the lower-lateral portion of the left breast consists of architectural distortion. There is also a group of microcalcifications close to the chest wall, within the same region where the architectural distortion is seen. Microfocus magnification images of the galactogram in the MLO (E) and CC (F) projections. The galactographic contrast medium outlines distended ducts and duct-like structures corresponding to the architectural distortion seen on the mammograms. The group of microcalcifications close to the chest wall are casting type, a mammographically malignant type. Breast MRI (G-I) images demonstrate a diffuse disease occupying an entire lobe between the nipple and the chest wall. The washout enhancement on MRI and the ultrasound images (J, K) show a microlobulated, oval-shaped tumour. Ultrasound guided 14G core biopsy (L). Histology of the 14G core specimen (M): poorly differentiated invasive carcinoma associated with Grade 3 “DCIS”. Our interpretation: Fluid producing duct forming invasive carcinoma of ductal origin producing neoducts through the process of neoductgenesis (DAB and ddDAB).

The positive 14G core biopsy and the diffuse nature of this extensive malignancy at imaging led to the decision to perform mastectomy. The specimen slice radiographs are correlated with detailed images from large format thin section histopathology in Figure 2.

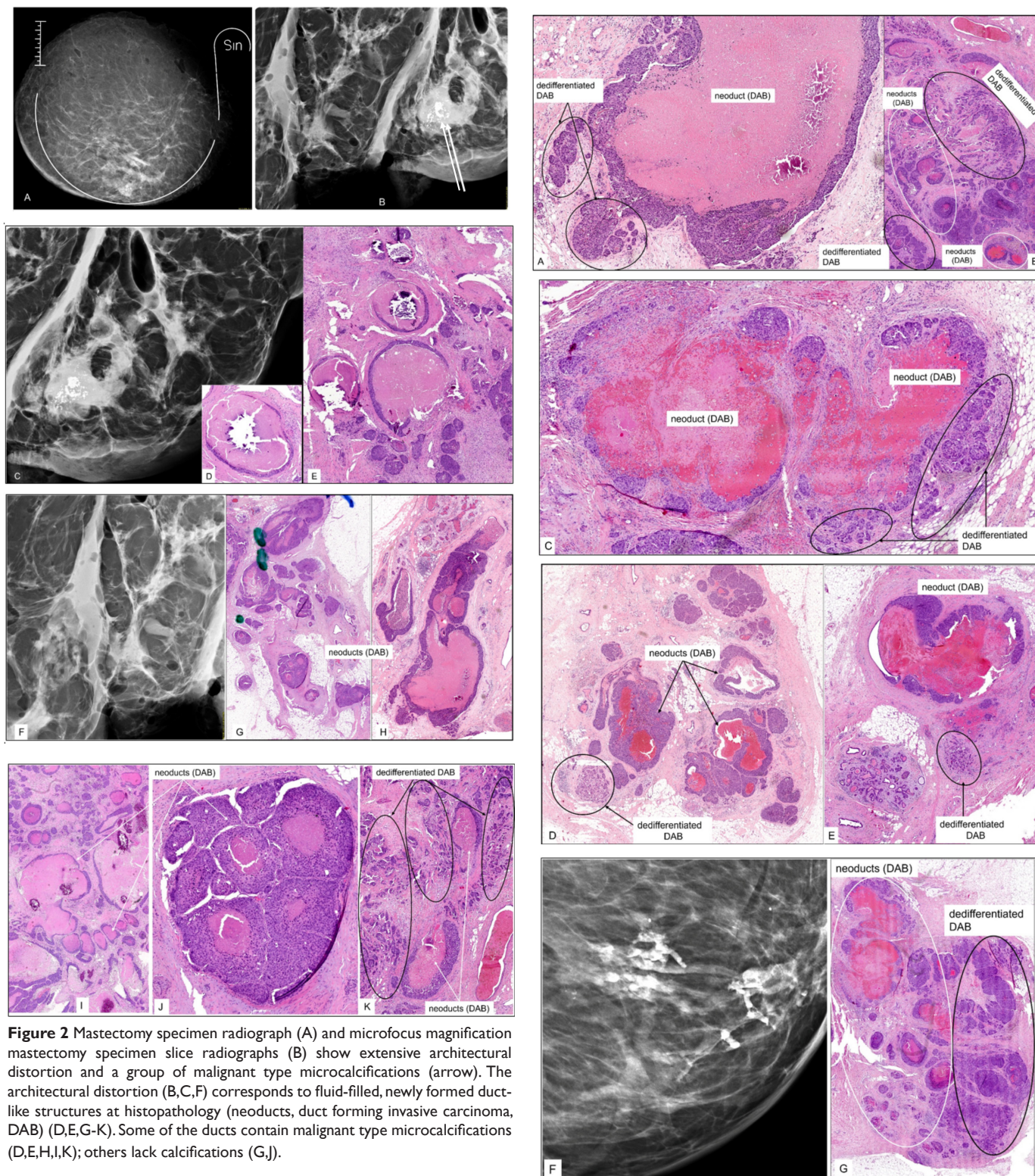


Figure 2 Mastectomy specimen radiograph (A) and microfocus magnification mastectomy specimen slice radiographs (B) show extensive architectural distortion and a group of malignant type microcalcifications (arrow). The architectural distortion (B,C,F) corresponds to fluid-filled, newly formed duct-like structures at histopathology (neoducts, duct forming invasive carcinoma, DAB) (D,E,G-K). Some of the ducts contain malignant type microcalcifications (D,E,H,I,K); others lack calcifications (G,J).

A series of detailed images from large format histopathology glass slides illustrate the close relationship between the cancer-filled neoducts (DAB, 2nd phase) and the dedifferentiated neoducts (ddDAB, 3rd phase) in this breast cancer originating in major lactiferous ducts (Figure 3 & 4).

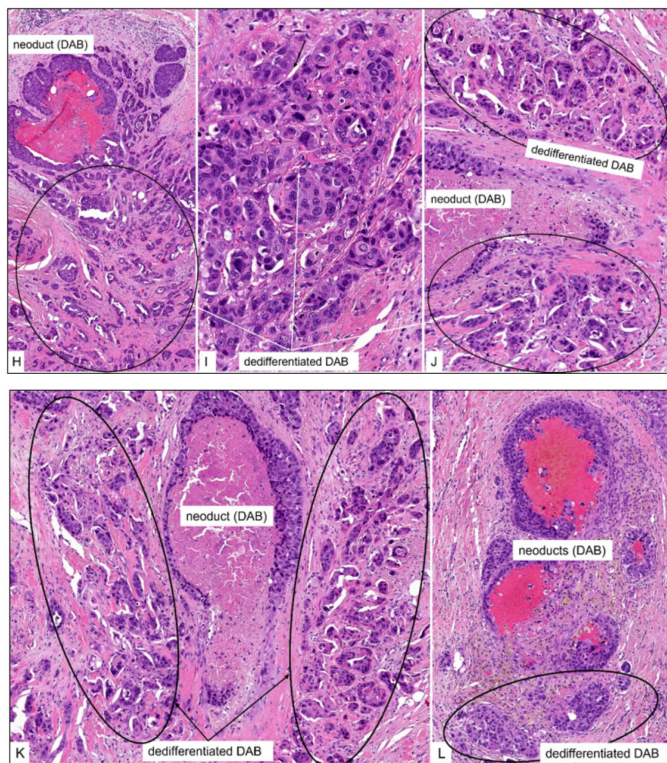


Figure 3 Histopathologic illustration (A-E, G, L) of two consecutive phases in the evolution of breast cancer originating in the major lactiferous ducts: 2nd phase (neoducts, DAB) and 3rd phase (dedifferentiated neoducts, ddDAB). The microfocus magnification galactogram (F) is a good presentation of the underlying histopathology.

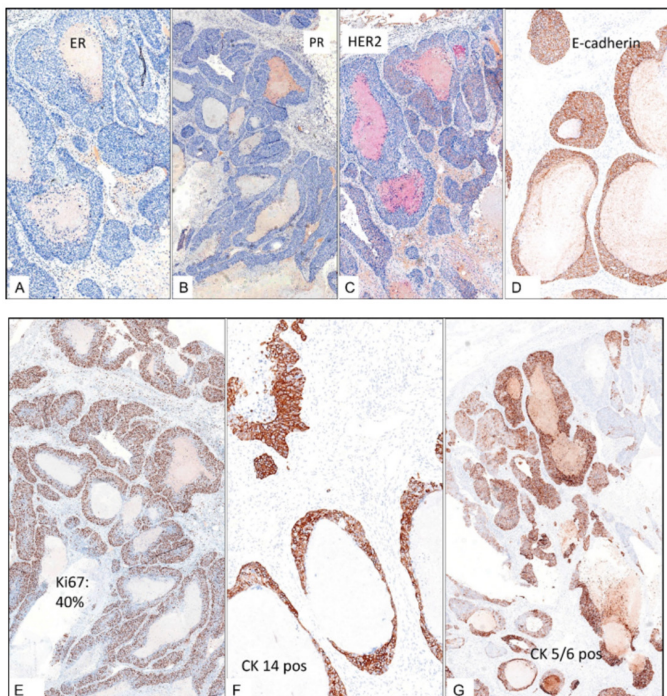


Figure 4 Immunohistochemical (IHC) biomarkers of the breast malignancy: ER/PR/HER2 negative (A-C) (triple negative tumour), E-cadherin positive (D), Ki 67 proliferation index 40% (E). CK 14 (F) and CK 5/6 (G) staining were positive, indicating a tumour with basal-like phenotype.

Follow-up: Three months following diagnosis and initiation of treatment the patient was diagnosed with lung metastases. Haematoxylin-eosin staining combined with IHC biomarkers confirmed that the recently diagnosed breast cancer had metastasized to the lungs (Figure 5).

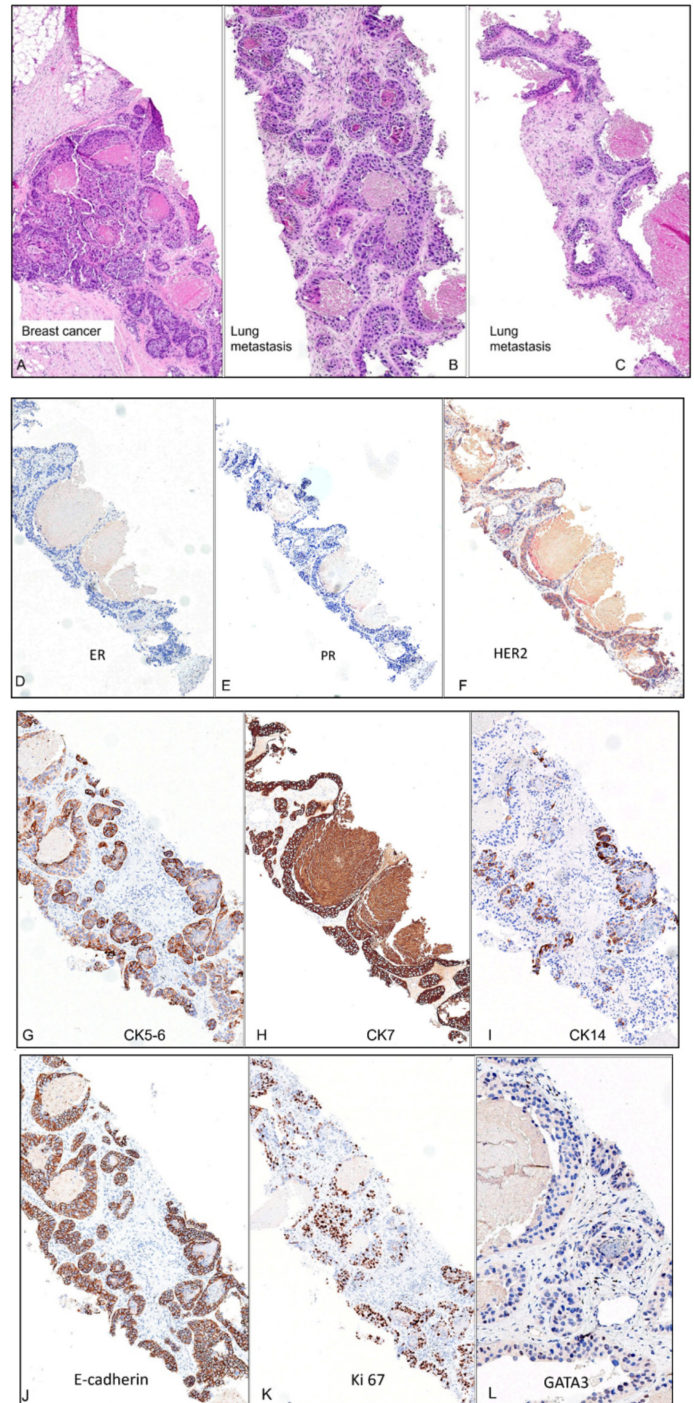


Figure 5 Haematoxylin-eosin (H&E) staining of the breast cancer (A) compared with the H&E- stained lung metastases (B, C). The pattern of the cancer-filled neoducts seen both in the lung metastases and in the original breast cancer is strikingly similar. The IHC biomarkers of the lung metastases show a triple negative tumour (D-F) with basal-like phenotype (G-I). E-cadherin was positive (J), the proliferation index (Ki67) was 40% (K) and the breast tissue marker, GATA3 (L) was slightly positive. The histopathologic findings and the IHC biomarkers of the lung metastases confirmed that the metastases were of breast cancer origin.

Outcome: Eight months after diagnosis and initiation of treatment the patient died. The official cause of death in the Death Registry is breast cancer.

Using the refined assessment of the cause of death: The patient died from the combined effects of cancer-filled neoducts (duct forming invasive carcinoma, DAB) and invasive dedifferentiated neoducts (ddDAB)

Second case

This 41-year-old asymptomatic woman was called back from mammography screening for assessment of the asymmetric density in the upper-outer quadrant of her left breast (Figure 6).

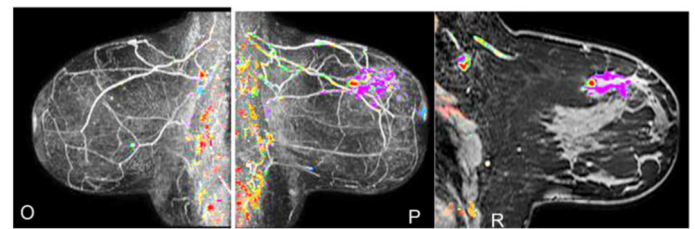
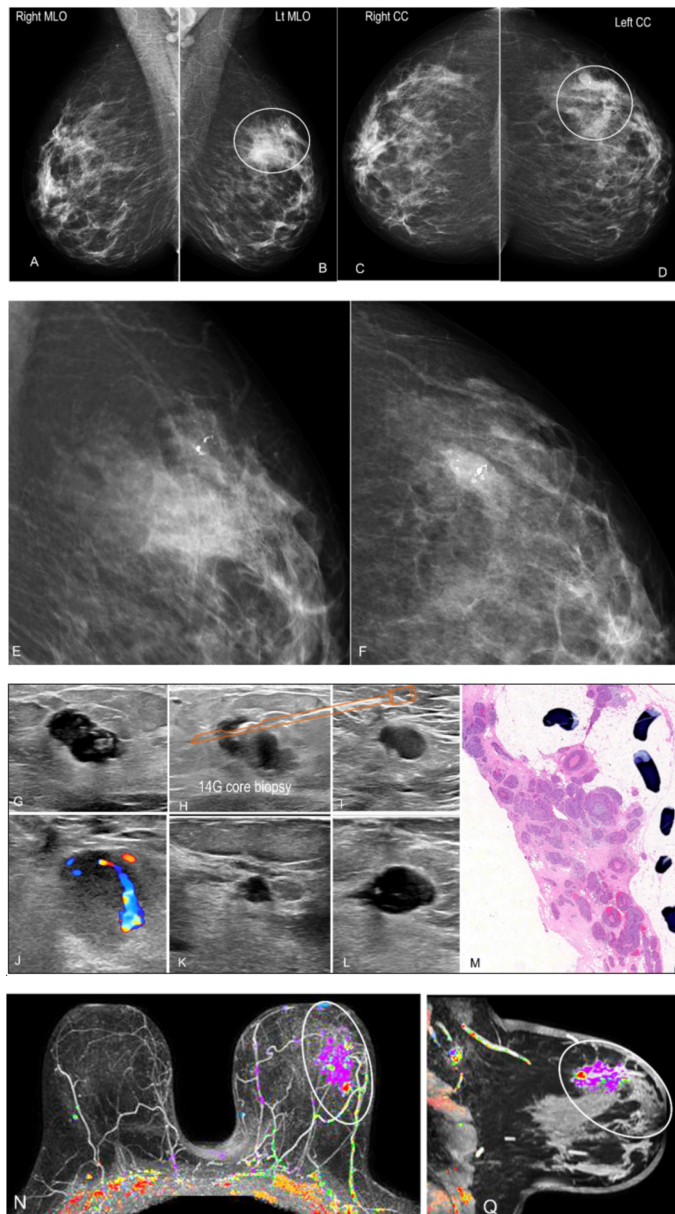
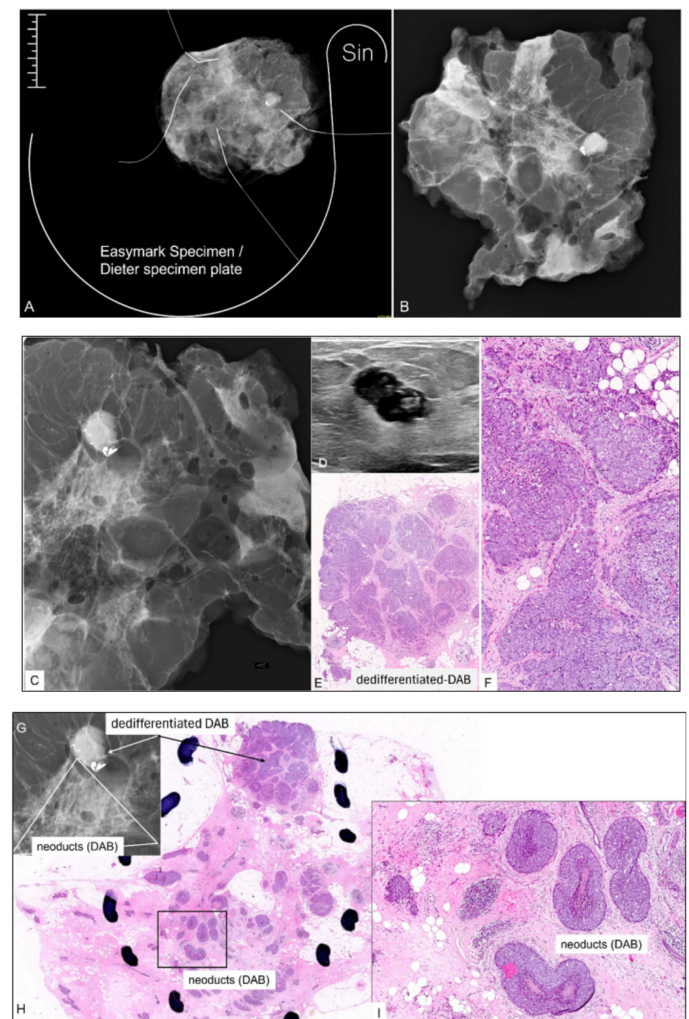


Figure 6 Medio-lateral (A,B) and cranio-caudal (C,D) mammograms. This asymptomatic woman was called-back for assessment of the nonspecific asymmetric density and the associated cluster of microcalcifications (encircled) detected on the screening mammograms of her left breast. MLO (E) and CC (F) microfocus magnification mammograms revealed an oval-shaped tumour mass containing a few malignant type microcalcifications. Hand-held ultrasound (G-L) showed multifocal tumours. The largest, oval, microlobulated malignant tumour mass measured 15x10 mm; the satellite tumours were smaller (6x5 mm, 5x5 mm, 3x3 mm). Histologic examination of the 14G core biopsy specimen (M) revealed cancer-filled neoducts (DAB). Breast MRI examination (N-R) showed extensive malignant disease over a region measuring 60x50 mm.

The tumour was localized with four wires and surgically resected. Imaging-histopathology correlation is shown in Figures 7–8. Further histopathology images are shown in Figure 9.



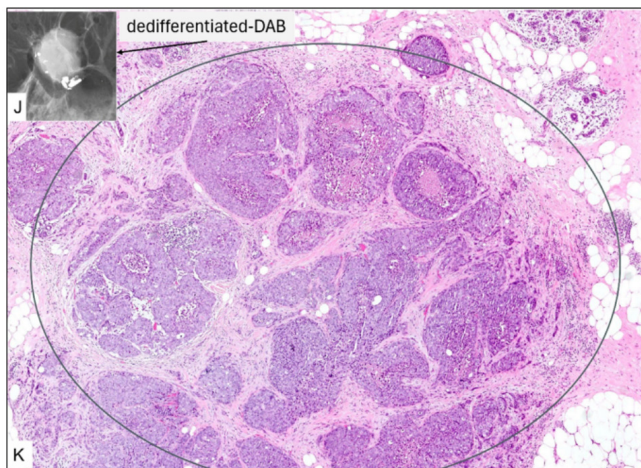


Figure 7 The surgical specimen was placed in the OR on the Easymark specimen/Dieter specimen plate (A). The microfocus magnification radiographs of the sliced specimen (B,C,G,J,L) are correlated with the large format thin section histopathology slide (E) and sections of these (F,H,I,K). The only finding on the ultrasound image and on the specimen radiographs is the solitary oval tumour mass, which corresponds to invasive dedifferentiated DAB at histopathology (E,F,H,K).

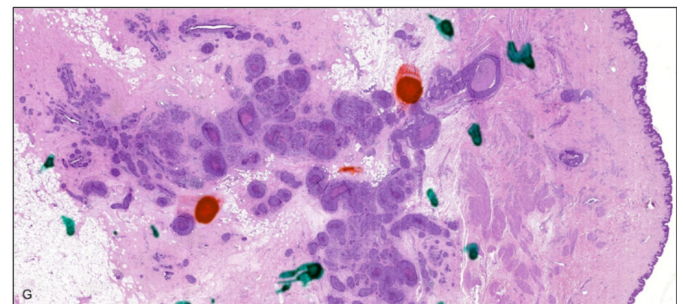
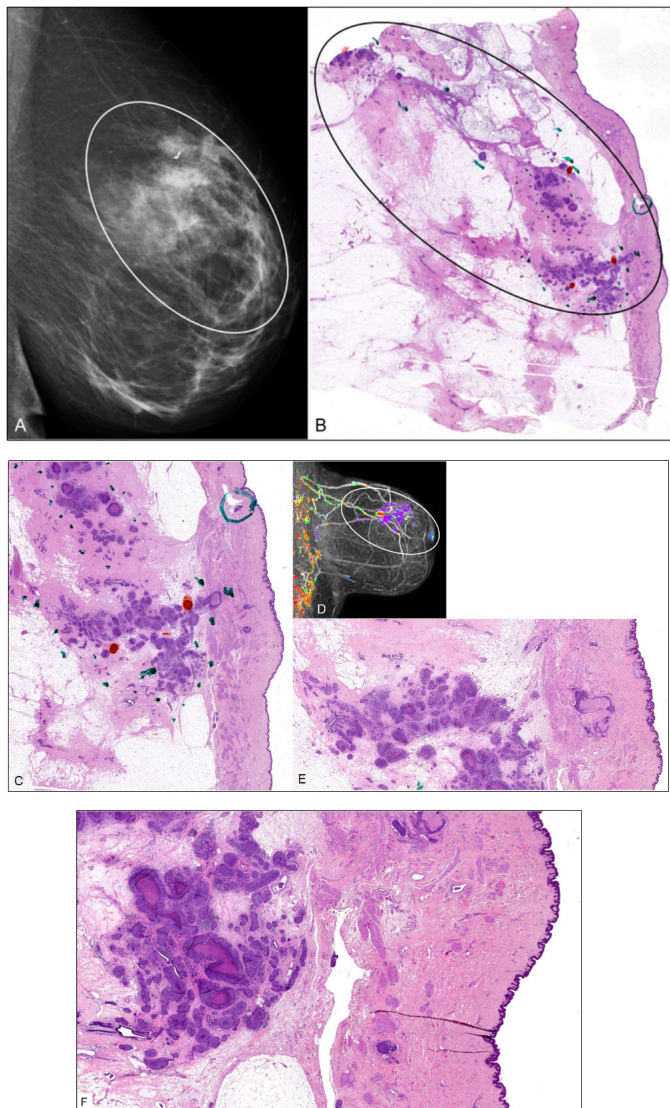
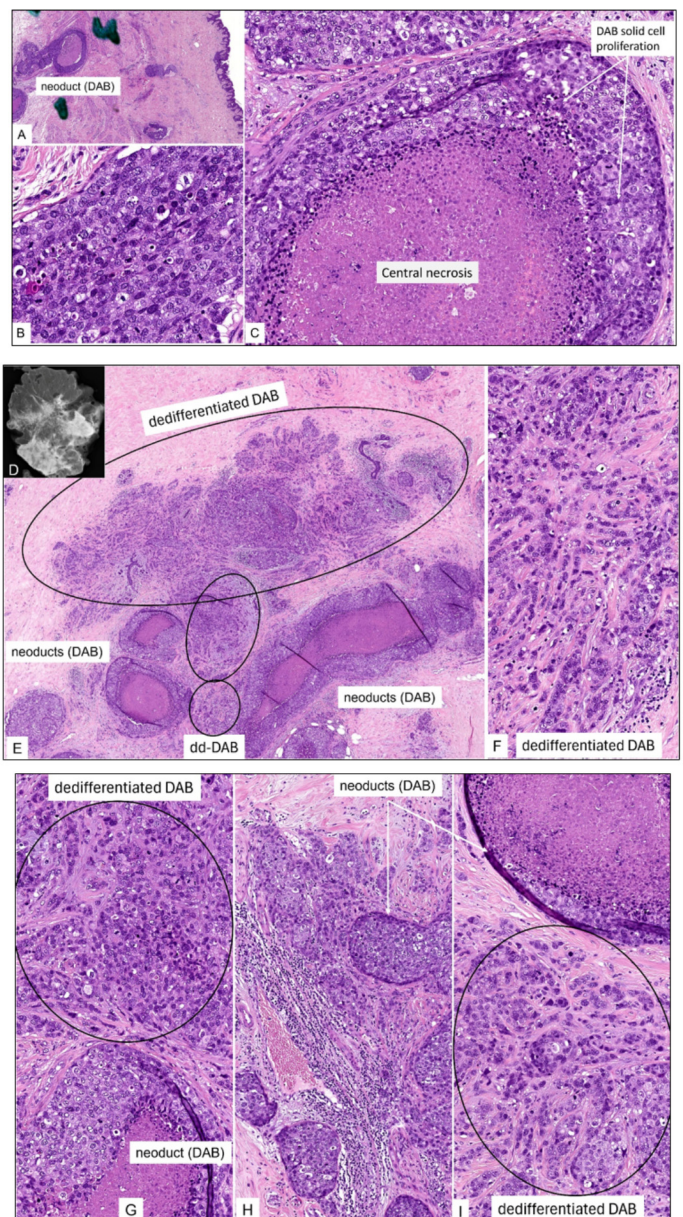


Figure 8 Correlation of the mammogram (A) and MRI (D) images with the large format thin section histopathology image (B) and detailed images (C,E,F,G). The disease extends between the chest wall and the nipple and is also seen within the nipple. Microscopic examination showed non-calcified neoducts (DAB) and invasive, dedifferentiated DAB over a region measuring 75x40 mm.



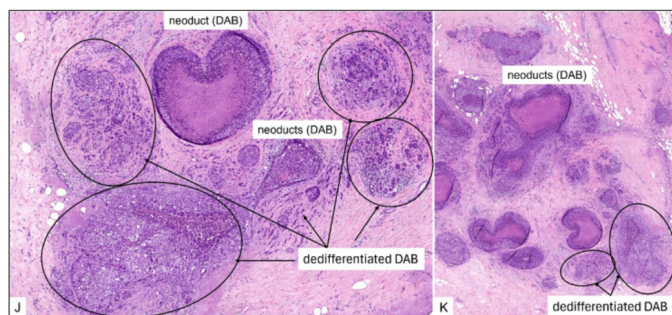


Figure 9 Low-power (A) and high-power histopathology images (B,C) show one of the retroareolar neoducts containing Grade 3 cancer cells and central necrosis. The non-specific density seen on the inserted specimen-slice radiograph (D) contains the mammographically occult extensive, non-calcified malignancy seen on the histology images (E-K), which illustrate both the cancer-filled neoducts (DAB) and the adjacent, extraductal cancer cells (ddDAB).

The IHC biomarkers of the invasive dedifferentiated DAB are shown on Figure 10.

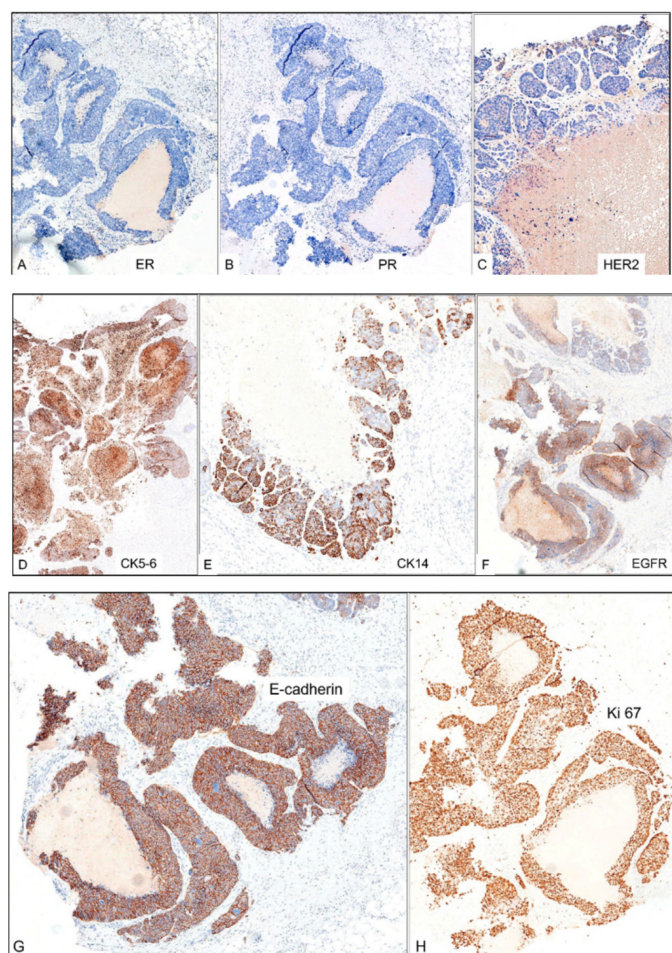


Figure 10 The tumour was ER, PR, HER2 negative (A-C) (triple negative). CK5-6 (D), CK 14 (E) and EGFR (F) positive tumour (basal-like phenotype). The tumour was E-cadherin positive (G) and had a high proliferation index (Ki67 75%) (H).

Ultrasound imaging-histopathological correlation of the axillary node metastases (Figure 11).

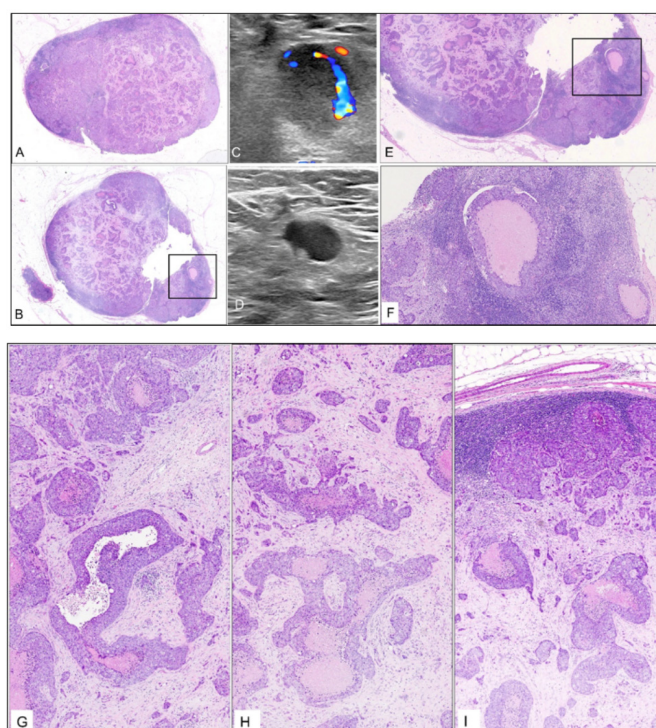
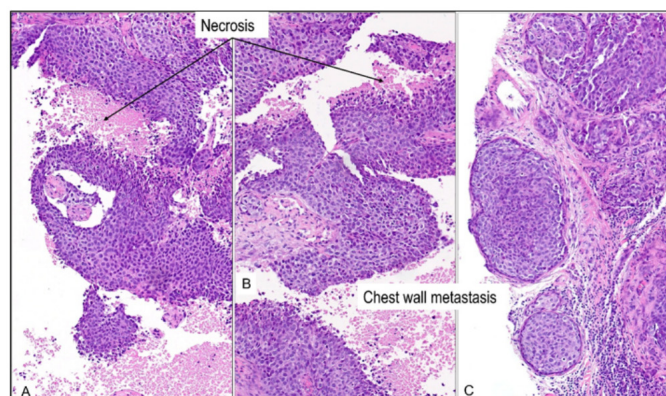


Figure 11: Ultrasound examination (C,D) showed pathologic axillary lymph nodes. Among the 14 surgically removed lymph nodes, two had extensive metastases (pN 2/14), both DAB and dedifferentiated DAB (A,B,E,F-I).

Final histopathologic diagnosis: Multifocal basal-like, triple negative dedifferentiated DAB foci measuring 15x10 mm, 6x5 mm, 5x5 mm, 3x3 mm associated with extensive Grade 3 neoducts (DAB). Total disease extent: 75x40 mm. The preoperative neoadjuvant chemotherapy had a barely noticeable effect on the malignant cells. Extensive LVI. pN 2/14.

Follow-up: Treatment started with chemotherapy, followed by segmentectomy six months later, and an additional one month later mastectomy was performed. One month after mastectomy the patient was diagnosed with a chest wall recurrence and a liver biopsy showed breast cancer metastases (Figures 12–14).



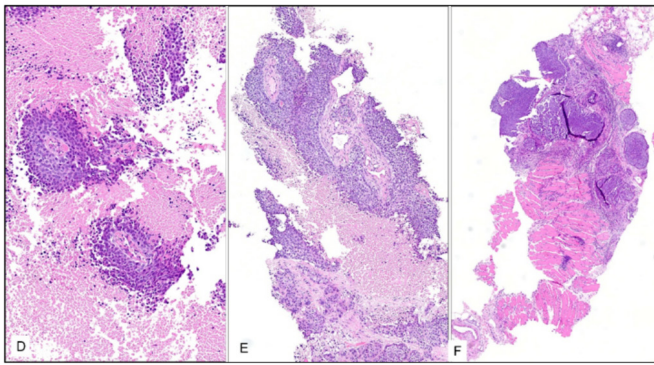


Figure 12: Neoduct-like cancer-cell formations in the chest wall metastases (A-F). Pectoral muscle invasion by the neoducts (F).

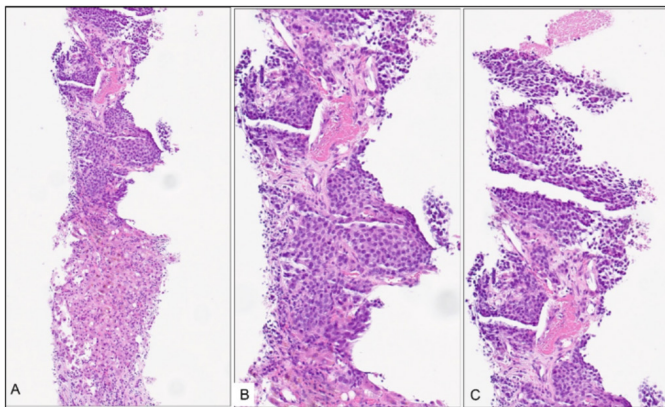


Figure 13: Dedifferentiated DAB-type cancer cells in the liver metastases (A-C).

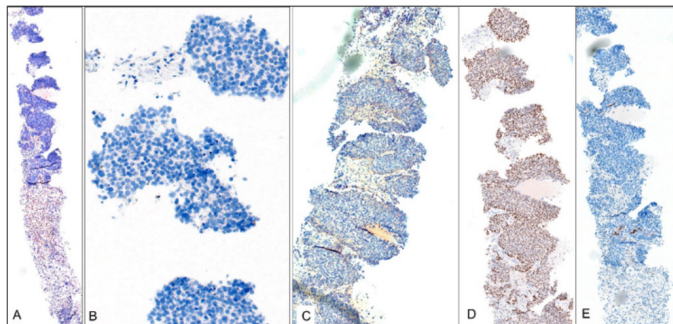


Figure 14: IHC biomarkers of the liver metastases: ER (A), PR (B), HER2 (C) negative, triple negative tumour metastasized from the breast to the liver. The metastases were GATA3 positive (D) and mammoglobin negative.

Outcome. Twelve months after diagnosis and initiation of treatment the patient died. The official cause of death in the Death Registry is breast cancer.

Using the refined assessment of the cause of death: The patient died from metastasizing ddDAB.

Discussion

A remarkable accomplishment of clinical cancer research during the past 50 years is the significant decrease in breast cancer deaths resulting from earlier diagnosis through organized mammography screening enabling treatment of breast cancer at an earlier phase.^{2,3} Despite these accomplishments over the past few decades, the remaining challenge is to recognize those breast cancers that are still fatal, even when women attend screening regularly and receive

modern therapeutic regimens.⁴⁻⁷ Our success or failure is largely dependent upon the part of the glandular tissue from which the breast cancer subtype originates.^{7,8}

Most of the fatal tumours come from the following categories: multifocal acinar adenocarcinoma of the breast (AAB), originating in multiple terminal ductal lobular units (TDLUs), diffusely infiltrating breast cancers originating in the major lactiferous ducts, and breast cancers originating in the stem cells of the mesenchyme (BCMO). Breast cancers originating in the major lactiferous ducts account for 10% of all breast malignancies, but they have a higher fatality ratio since 20% of all breast cancer deaths occur among these malignancies. They have easily recognizable imaging biomarkers. Their recognition is important since they reliably indicate the site of tumour origin and have documented prognostic value.^{1,8,9}

Our focus in this presentation is on the cancers originating in the major ducts. Their pathogenesis is complex, consisting of three phases of evolution. In the 1st phase the cancer cells appear to arise from the stem cells of the major lactiferous ducts,^{1,8,10-14} and the proliferating aggressive cancer cells propagate within the preexisting duct, distending it considerably. This phase can be considered ductal carcinoma in situ, although at this point there are still no imaging signs. The 2nd phase of evolution is the new duct formation, neoductgenesis, “in which differentiated ductal epithelium dedifferentiates, detaches from the adjacent epithelial cells, penetrates the basement membrane (BM) and invades into the surrounding tissue”.⁸⁻¹⁰ They form new, haphazard, disorganized duct-like branching structures, neoducts. Some of the cancer cells acquire fibroblast-like phenotype through a process morphologically compatible with epithelial-mesenchymal transition (EMT), forming the periductal desmoplastic reaction. Neoducts can also be found in axillary lymph node metastases and in metastases to organs such as the liver, lungs and brain, as well as to the skeleton, etc.^{7,14} Although neoducts exhibit locally aggressive growth and true metastatic potential characteristic of duct forming invasive carcinomas, current histopathologic terminology still classifies these lesions as DCIS. We have proposed that these neoducts be termed ductal adenocarcinoma of the breast (DAB).^{1,8-10,14}

Associated with the neoducts, we frequently observed an infiltrating carcinoma in the adjacent extraductal parenchyma, indicating that the cancer progressed to the 3rd, more fatal phase. This final step of evolution shows structural dedifferentiation compared with 1st and 2nd phase since the cancer cells have spread from the neoducts through focal defects in the integrity of the neoduct boundaries and propagate freely throughout the interstitial spaces of the surrounding parenchyma with few boundaries. We suggest using the term dedifferentiated ductal adenocarcinoma of the breast (ddDAB) to define these invasive neoplasms.¹ The combination of DAB (neoduct) and the dedifferentiated DAB (ddDAB) shows an unexpectedly high fatality.^{1,7,9}

Conclusion

Imaging biomarkers enable the identification of a special, aggressive form of breast cancer arising within the major lactiferous ducts. Large format thin section histopathology can illustrate all three phases of the evolution of breast cancer originating in the major ducts. So long as the cancerous process occupies only the pre-existing ducts (1st phase), then the correct term is DCIS. Unfortunately, breast imaging does not recognize this phase of evolution; it cannot detect this breast cancer subgroup until the 2nd phase, when the carcinogenic process of neoductgenesis produces new, duct-like structures, presenting on the mammogram as malignant type calcifications or non-calcified architectural distortion. At this 2nd phase we propose

a new term for this duct forming invasive carcinoma, composed of neoducts produced through the process of neoductgenesis, ductal adenocarcinoma of the breast (DAB). Conventional histopathology uses the term ductal carcinoma in situ (DCIS) to describe this invasive 2nd phase, which is no longer *in situ* because the cancerous process is within the cancerous process is within disorganized, newly formed invasive neoducts, which can metastasize to lymph nodes and to distant organs.¹⁴ Detailed histopathologic examination demonstrates the structural dedifferentiation of this special form of stem cell carcinoma from the 1st phase, DCIS, to the 2nd phase, DAB, and to the 3rd phase, termed dedifferentiated ductal adenocarcinoma of the breast (ddDAB). In the 3rd phase the cancer cells are extraductal with no surrounding tubule-formation/duct-like structure. Documentation of neoducts in distant metastases calls for re-evaluation of the term DCIS when applied to these malignant neoducts.^{1,8,14} Use of accurate terminology could facilitate new research projects to help improve the outcome of patients diagnosed with cancers originating from the major lactiferous ducts.

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.

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