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Multifocal and diffusely infiltrating breast cancers are highly fatal subgroups needing further improvement in diagnostic and therapeutic strategies

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ABSTRACT

Physicians treating breast cancer patients often wonder why this dreaded disease is still fatal in some women despite our best diagnostic and therapeutic efforts. Our own studies on prospectively documented cases spanning several decades have given us new insights for approaching this problem. By using imaging biomarkers to classify breast cancer subtypes according to their apparent site of origin, we found that a majority of breast cancer deaths (71%) occur in a minority of breast cancers (45%). Breast cancer deaths are significantly more likely to occur in women with multifocal acinar adenocarcinoma of the breast, AAB (13.1%), diffusely invasive breast cancers of ductal origin, DAB (24 %) and breast malignancies of mesenchymal hybrid cell origin, BCMO (33.7%) compared with women having unifocal invasive breast cancers (6.1%). Preventing more of these fatal events will require a re-evaluation of the current imperfect histopathologic terminology of breast cancer with special attention to the diffuse breast cancer subtypes, intensification of multimodality imaging and multidisciplinary management, as well as application of image guided large format histopathology.

1. Why do women still die from breast cancer?

Regular mammography screening can detect a high proportion of preclinical, non-palpable breast cancers, and has brought us to a new era in the diagnosis and treatment of the disease. Although regular participation in organized mammography screening combined with modern therapeutic regimens has accomplished a decrease of about 50% in breast cancer deaths in asymptomatic women aged 40–69 years [1], we need to answer this question, "Why do women still die from breast cancer, even if they regularly participate in screening and receive modern therapy"? Part of the answer is that both research and clinical practice tend to view breast cancer as a single tumour mass and give too little attention to the tumour growth patterns (unifocal, multifocal, diffuse) of breast cancer subtypes. To gain further insights into this important issue, we investigated a comprehensive database which included all histologically proven invasive breast cancer cases (n = 2,425), both clinical and screen-detected, in women of all ages diagnosed at the Department of Mammography, during the years 1996–2014 and followed up to December 31st 2019. We classified these cancers into their apparent site of origin; unifocal acinar adenocarcinoma of the

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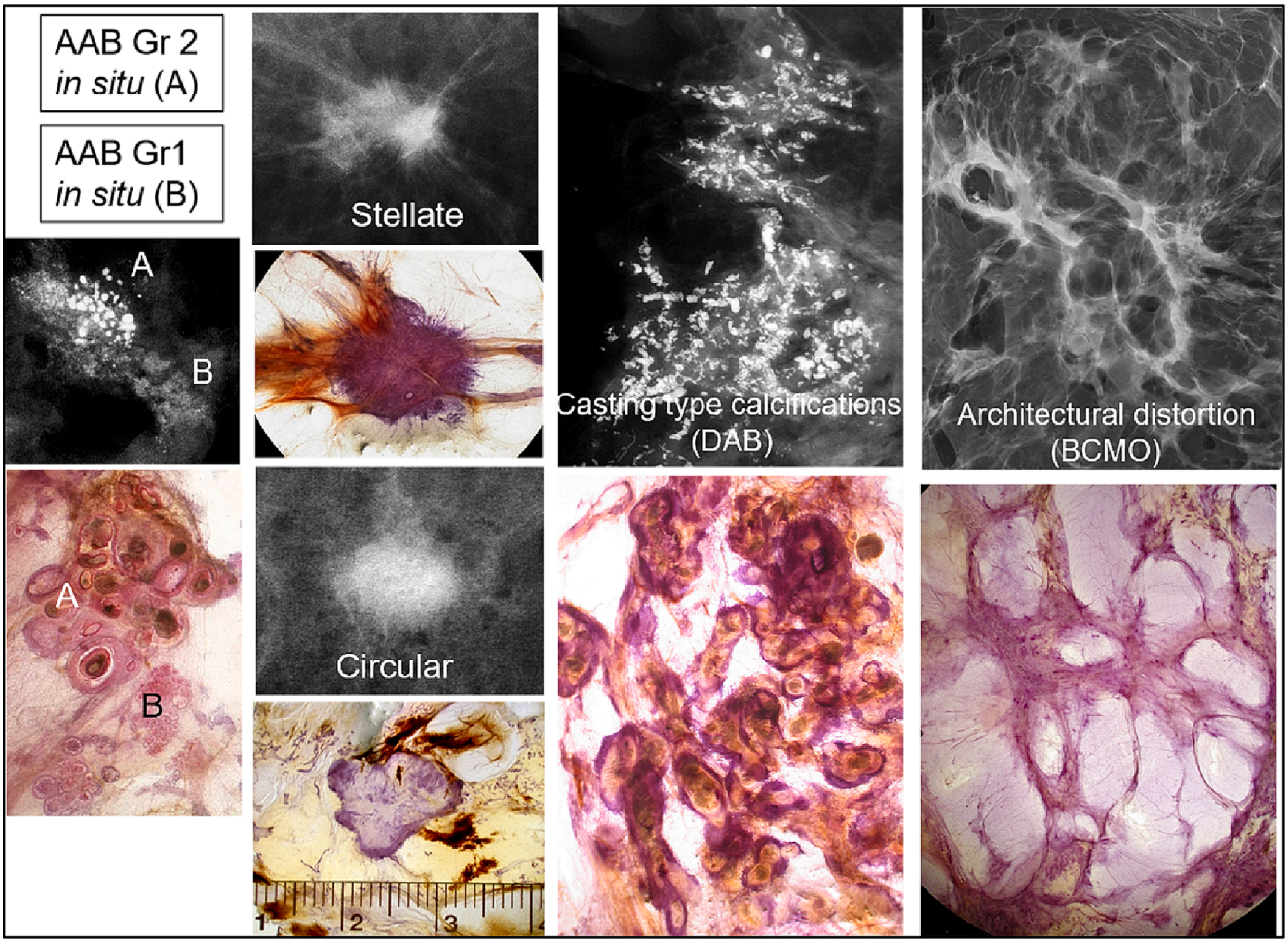


Fig. 1. Representative examples of the imaging biomarkers correlated with their corresponding histopathologic images.

breast (AAB), ductal adenocarcinoma of the breast (DAB) and breast cancer of mesenchymal origin (BCMO) [2]. Of these, 1,339 women had unifocal AAB, 680 had multifocal AAB, 237 had DAB and 139 had BCMO. The cases were prospectively classified according to tumour growth pattern (unifocal, multifocal and diffuse) and imaging biomarkers [2–6]. Large format thin section histopathology [7–10] was correlated with multimodal imaging findings [8–16] to help evaluate the full extent of multifocal and diffuse breast cancers and their surgical resection margins. The large format histopathology glasses were scanned at a resolution of 0.40 μm on a LE120 slide scanner (Huron Digital Pathology, St. Jacobs, ON, Canada). The Kaplan-Meier method was used to plot the cumulative survival of breast cancer patients stratified by imaging biomarkers and tumour growth pattern as unifocal AAB, multifocal AAB and diffuse breast cancers (DAB and BCMO).

Fig. 1 shows the four imaging biomarkers of *in situ* and invasive acinar adenocarcinoma of the breast (AAB); casting type calcifications, the most frequent form of ductal adenocarcinoma of the breast (DAB); and architectural distortion, the imaging biomarker of breast cancer of mesenchymal origin (BCMO).

Fig. 2 shows the tumor growth patterns / distribution of breast cancers.

Fig. 3 shows the frequency of breast cancer cases and breast cancer deaths in the combined multifocal and diffuse breast cancers (A, B), and in the four tumour growth pattern subgroups separately (C, D), all during the era of screening and the use of modern therapeutic methods.

These data emphasize the need to focus attention upon the more fatal multifocal and diffusely infiltrating breast cancer subtypes. Multimodality imaging and imaging biomarkers combined with image guided large format histopathology should be used to improve their management and outcome [17].

Earlier diagnosis with mammography screening and multimodality imaging does not appear to have affected the frequency of multifocal

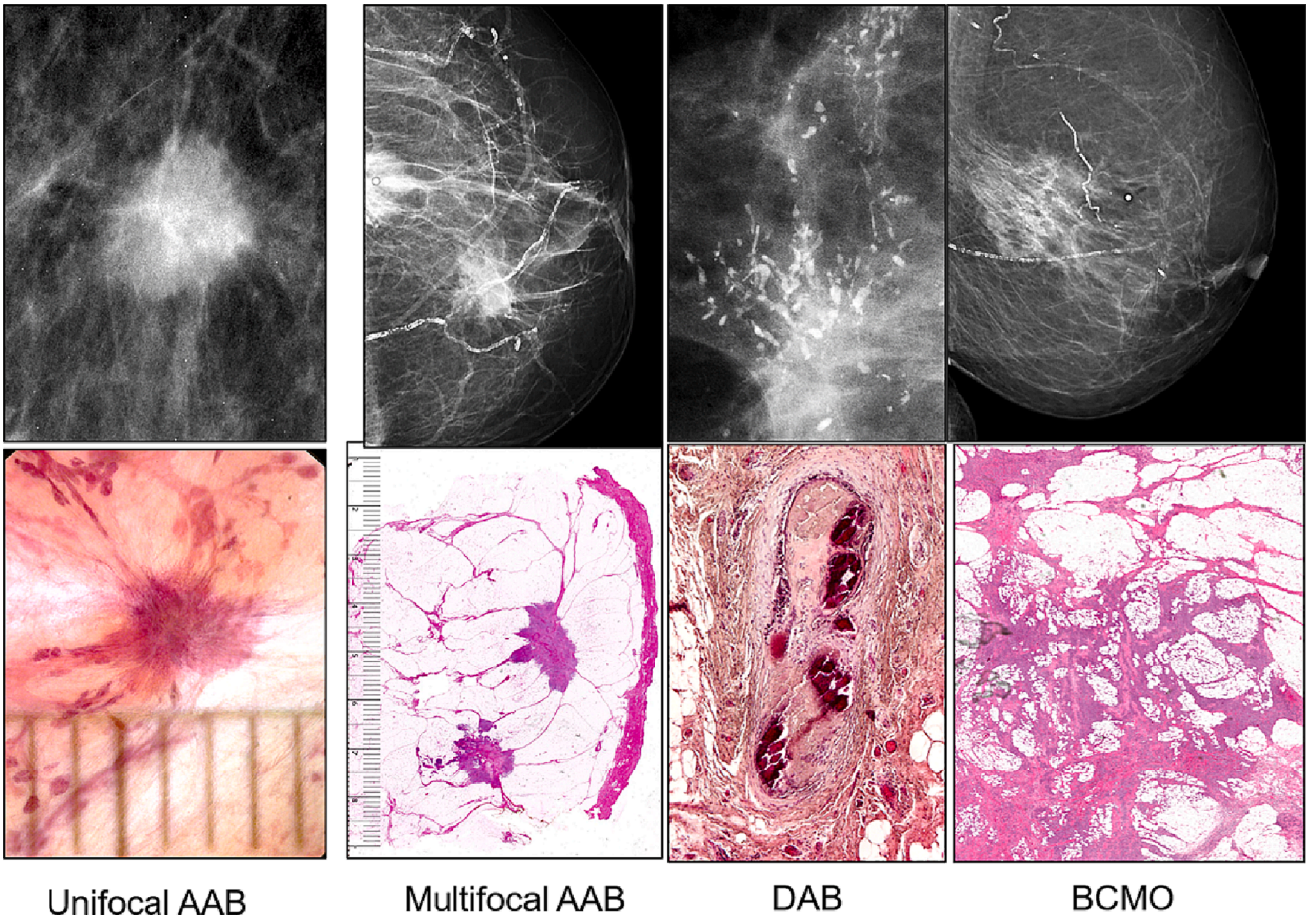


Fig. 2. Presentation of the four tumour growth patterns: unifocal AAB, multifocal AABs and diffuse breast cancers (DAB and BCMO).

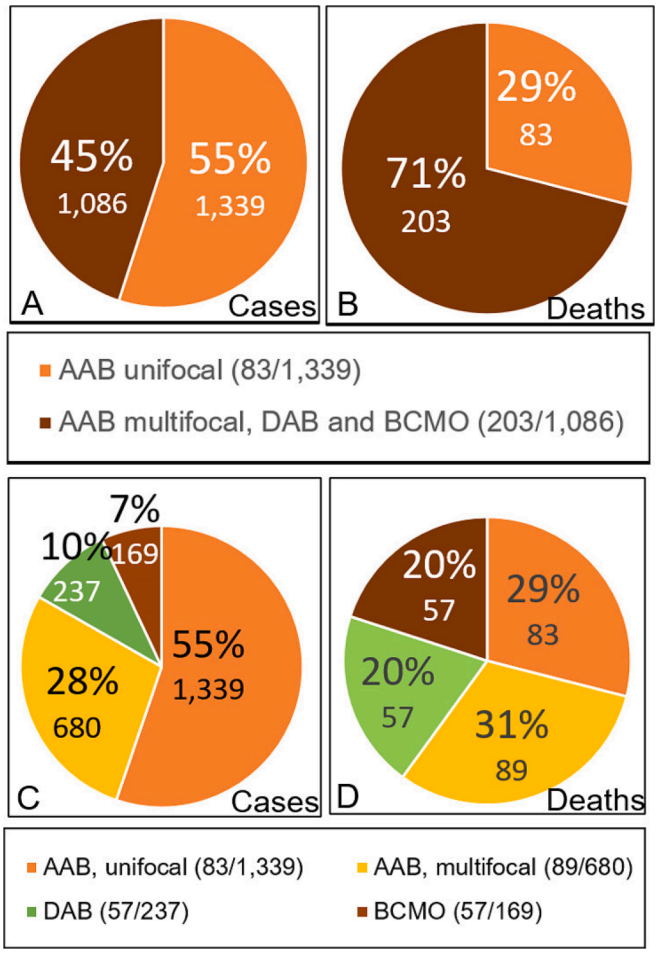


Fig. 3. Distribution of breast cancer cases (A,C) and breast cancer deaths (B,D) according to tumour growth patterns: unifocal, multifocal and diffuse (DAB, BCMO). Of the 2,425 invasive breast cancer cases in women of all ages, 1,339 were unifocal AAB, 680 were multifocal AAB, 237 were DAB and 139 were BCMO. Figs. A-B illustrate the frequency of cases (45%) and deaths (71%) in the combined multifocal and diffuse breast cancer tumour growth patterns. Figs. C and D show the frequency of cases and deaths in the four groups separately.

and diffusely invasive breast cancers (Fig. 4) [18–20].

Although mammography screening and multimodality imaging are bringing tumours to surgery at an earlier phase of their development, the high, unchanged frequency of multifocal and diffuse breast cancers emphasizes the need for careful evaluation of the full tumour extent when planning breast conserving surgery. The non-palpable tumours are not necessarily limited to a smaller region in the breast. To justify breast conserving surgery, these non-palpable, early phase breast cancers also require a comprehensive preoperative multimodal imaging evaluation to determine their unifocal, multifocal and diffuse nature. The TNM policy of relying upon the diameter of the largest invasive focus in multifocal AABs underestimates their actual tumour burden [3]. More importantly, the two diffusely infiltrating breast cancer subtypes, those originating in the major lactiferous ducts (DAB) [4,5] and those conventionally termed invasive lobular carcinoma (BCMO), have an even higher fatality rate (Fig. 5) [6,11,21].

2. Multifocal acinar adenocarcinoma of the breast (AAB) – the harmfulness of multifocality

Women with multifocal invasive AAB have a significantly poorer survival than those with unifocal AAB. Multifocality is an independent, negative prognostic factor [18,20,22–24]. When matching the tumour size, histologic malignancy grade, imaging biomarkers and immunohistochemical biomarkers of the unifocal cancer cases with the same parameters of the largest focus of multifocal invasive breast cancers, the fatality rate is significantly poorer for the multifocal cases [3]. This confirms that the multifocal nature is the overriding prognostic factor, which can only be due to the greater tumour burden of multifocal tumours. The tumour burden of unifocal cancers can be estimated in terms of either tumour diameter, surface area or volume, although the commonly used tumour diameter does not necessarily give a reliable estimate of the actual tumour burden. Complicating factors such as central necrosis, mucin or fluid content, and intratumor heterogeneity can affect measurement reliability. A promising approach is the determination of the tumour surface area [25]. There is no reliable consensus for the estimation of the tumour burden in multifocal AABs, due to inhibiting factors such as intra- and intertumoral heterogeneity and associated occult foci.

The significant harmful effect of multifocality makes determination of tumour growth pattern (unifocal, multifocal, diffuse) and disease extent by multimodality imaging an issue of utmost importance.

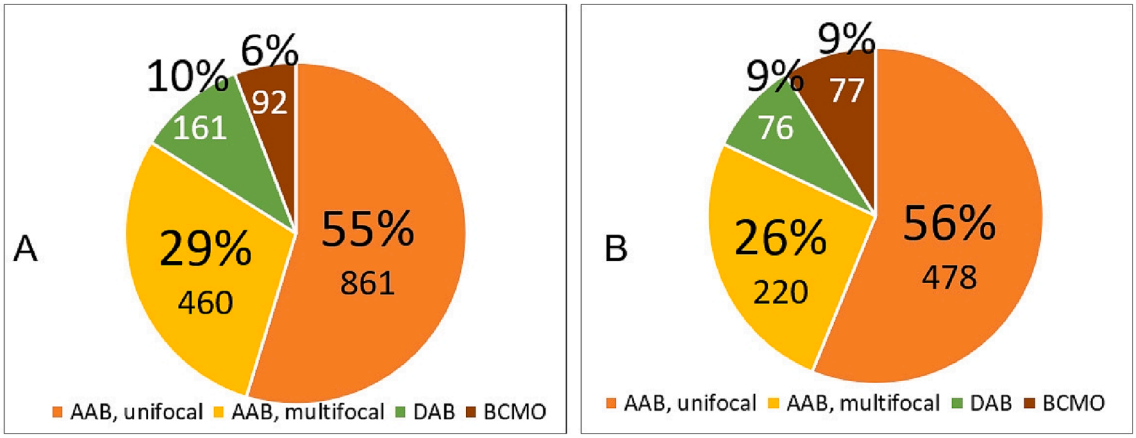


Fig. 4. Distribution of breast cancer cases according to tumour growth patterns, unifocal, multifocal and diffuse (DAB, BCMO) in the screening age group 40–69 years (A) and in women $<$ 40 and $\geq$ 70 years of age (B).

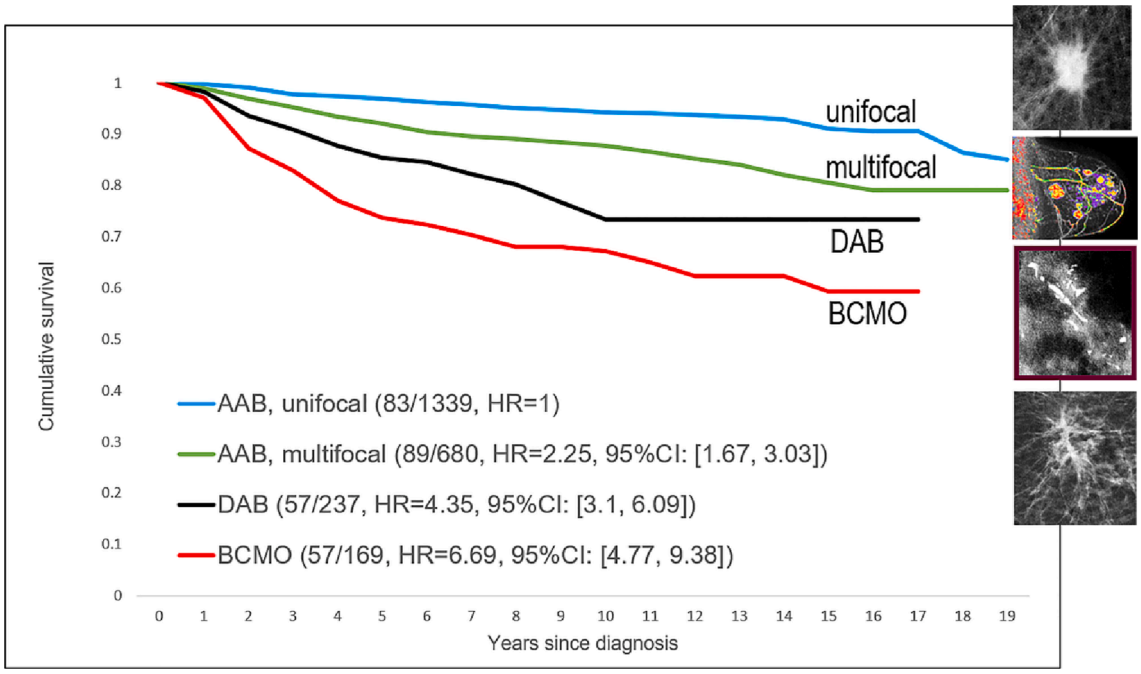


Fig. 5. Long-term survival of women diagnosed from 1996 to 2014 with invasive breast cancer and followed up to the end of 2019. Dalarna county, Sweden. Women with multifocal AAB and the diffusely infiltrating breast cancer subtypes (DAB and BCMO) have a significantly poorer long-term outcome compared with women having unifocal AAB.

Correlation of the preoperative multimodality imaging findings with the postoperative large format, thin section histopathology findings provide a reliable estimate of disease extent in women with multifocal AAB (Fig. 6).

3. Diffuse breast cancer originating from the major lactiferous ducts (DAB), unexpectedly fatal

This subgroup of breast cancers is characterized by neoductgenesis, in which newly formed duct-like structures invade the surrounding tissue, resulting in a massive tumour burden with a high fatality rate [4,5,26–28]. It has very specific and easily recognizable imaging biomarkers indicating its presence [5]. The current histopathologic diagnostic terminology, ductal carcinoma *in situ* (DCIS), does not account for the high fatality rate of DAB and is detrimental to its management as it underestimates the severity of the disease. Consequently, surgeons tend to favour breast conserving surgery which often fails to remove the entire, aggressive malignancy [5,29]. The pathology guidelines do not recommend performing HER-2 staining on the allegedly "*in situ*" component [30,31], and oncology guidelines do not recommend administering Herceptin treatment to patients with "DCIS", even if it is HER-2 positive [32]. These management constraints all lead to underdiagnosis and undertreatment of women with this highly malignant disease and are likely to contribute to the poor outcome seen on Figs. 3 and 5. The DAB usually coexists with AAB tumour(s), but the management decisions are guided by the less fatal AAB component, without sufficient consideration given to the DAB component. In particular, the IHC biomarkers are not determined from the DAB component when there is an associated AAB.

Fig. 7 shows the case of a 51-year-old woman, who was treated with irradiation and chemotherapy for Hodgkin's disease 21 years earlier, at the age of 30. The mammograms show malignant type calcifications in the right retroareolar region as well as in the right upper-outer quadrant. Large format thin and thick section histopathology examinations document extensive, fluid producing carcinoma originating in the major lactiferous ducts (DAB), extending through the Cooper's ligaments and subcutaneous tissue to the skin. This case illustrates how preoperative, comprehensive multimodal imaging should be used to reveal such tumour spread when planning subcutaneous, skin and/or nipple-sparing mastectomy [2,4,5]. Additional DAB cases are shown on Figs. S1-S3.

4. Diffusely infiltrating breast cancer, termed "diffusely infiltrating lobular carcinoma", the most fatal subtype

This breast cancer subtype has an incidence of 5–8%, but the risk of dying from it is approximately 40% (Fig. 5) and this poor outcome has not changed over several decades [2,6,11,21]. It has characteristic clinical, imaging, and histopathologic features that are quite different from the breast cancer subtypes that originate from either the acini of the lobules (AAB) or from the major lactiferous ducts (DAB). The

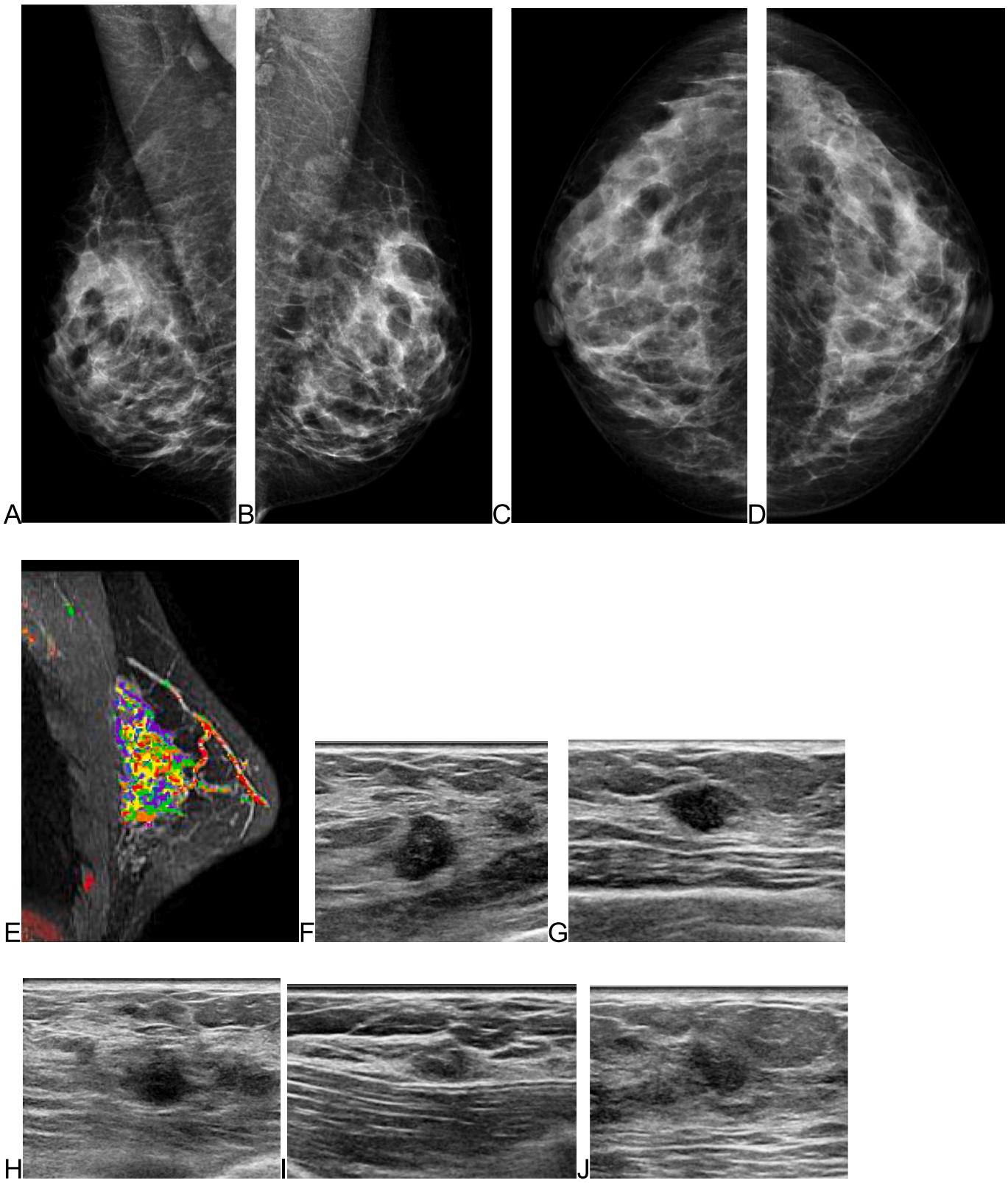
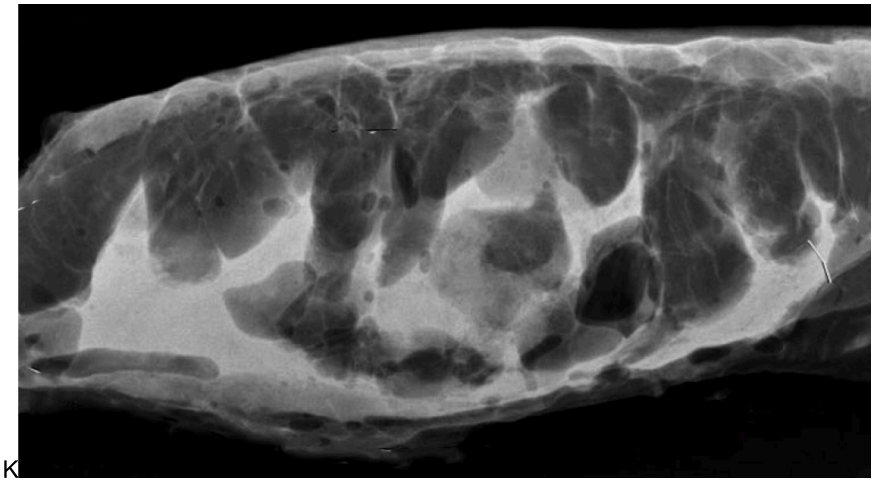
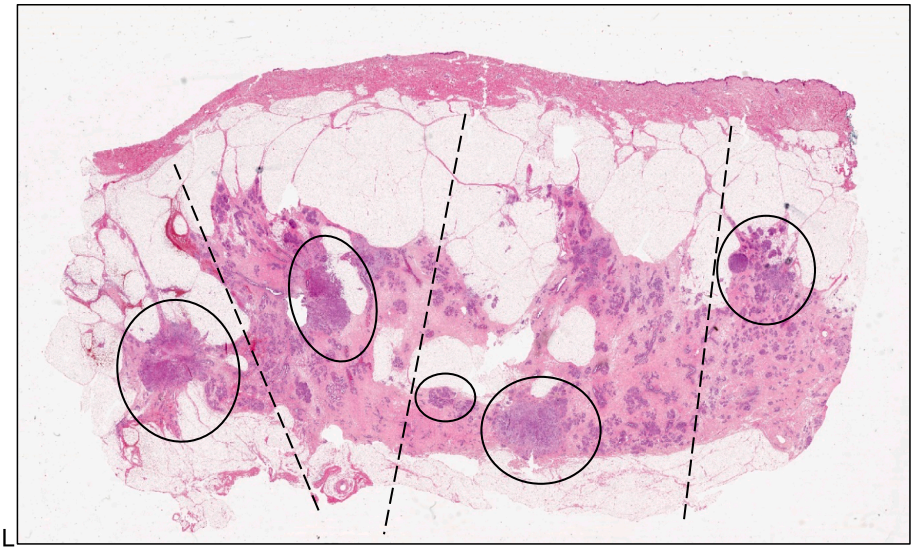


Fig. 6. MLO (A,B) and CC (C,D) projection mammograms of a 35-year-old woman with a self-detected retraction of the skin over the lower-outer quadrant of the left breast. There is no mammographic evidence of a tumour mass, microcalcifications or architectural distortion in the heterogeneously dense breasts (BI-RADS C). Breast MRI (E) shows non-mass enhancement over a region measuring 45x15x65 mm. Hand-held ultrasound examination reveals multiple tumour foci (F-J), the largest measuring 10 mm. Microfocus magnification specimen slice radiographs (K,M) are correlated with large format thin section histopathology images (L,N). The individual invasive AAB foci are encircled and potential surgical resection lines are indicated by the dashed lines. Final histopathologic diagnosis: multifocal (7 individual foci) poorly differentiated AABs, the largest focus measuring 11x8 mm associated with extensive Grade III DAB. Total disease extent: 75x38 mm. Biomarkers: ER/PR positive, HER2 + ve, Ki67 39%. LVI.



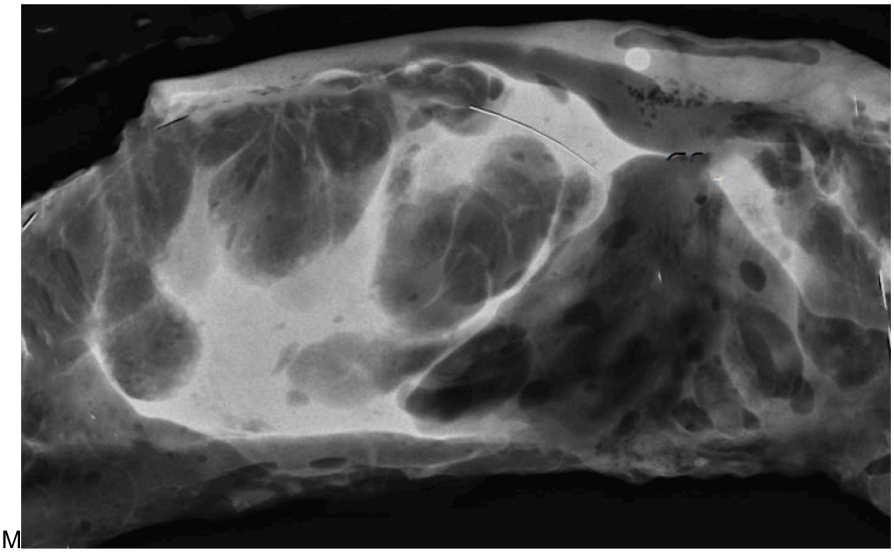
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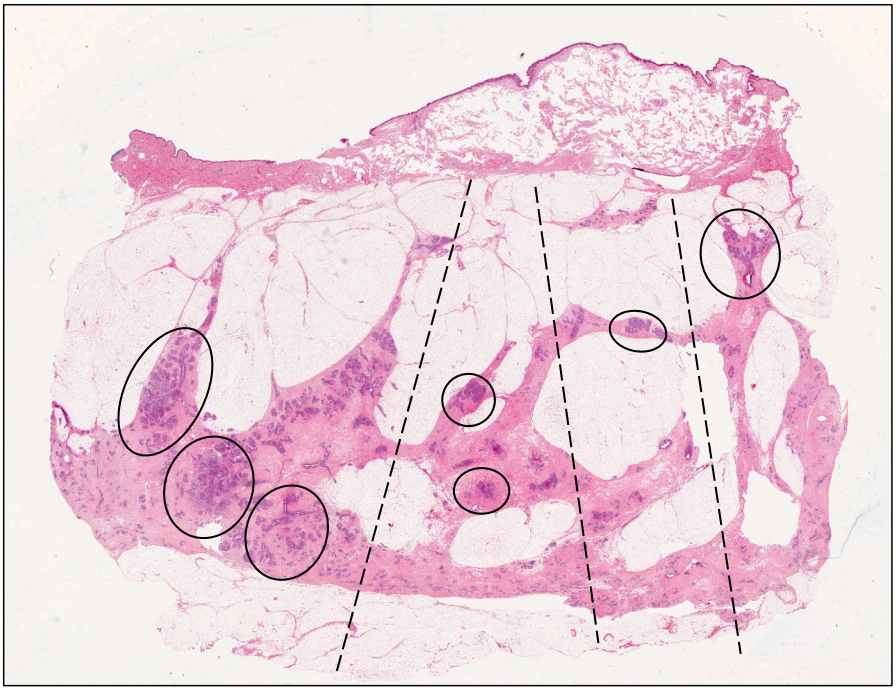


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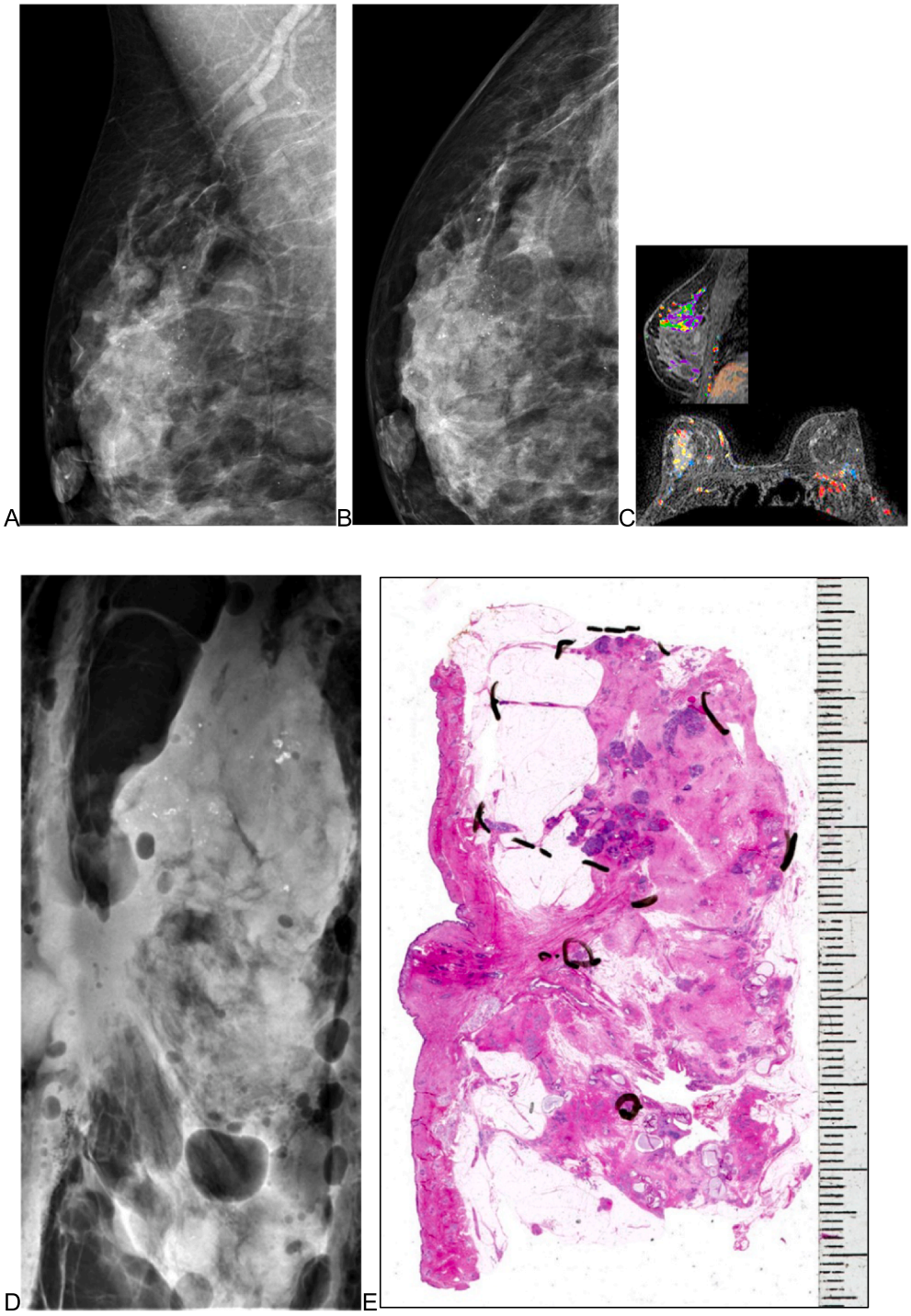


Fig. 7. Details of the right MLO (A,B) projections showing dense breast parenchyma (BI-RADS D) and faint, skipping stone-like calcifications with no associated tumour mass. The MRI images (C) illustrate non-mass enhancement throughout the entire lobe, documenting the extensive nature of this breast malignancy. Microfocus magnification of a mastectomy specimen slice radiograph (D) correlated with large format thin section histopathology (E) confirms that the carcinoma extends to the posterior margin, to the skin and to the nipple. Intermediate power histopathology images of the involved Cooper's ligaments demonstrate the malignant process (F,G). An additional specimen slice radiograph (H) and corresponding low power (I) and intermediate power (J) large format histopathology demonstrate extensive neoductgenesis and an extention to the skin. Low power histopathologic image of the subcutaneous tissue revealed a conglomerate of neoducts right under the skin (L). The area in the rectangle in (K) is shown on intermediate and high power images (L). Final histopathologic diagnosis: 75 × 36 mm region with Grade 1–3 cancer originating in the major lactiferous ducts (DAB) with no associated acinar adenocarcinoma of the breast (AAB). pN0/2.

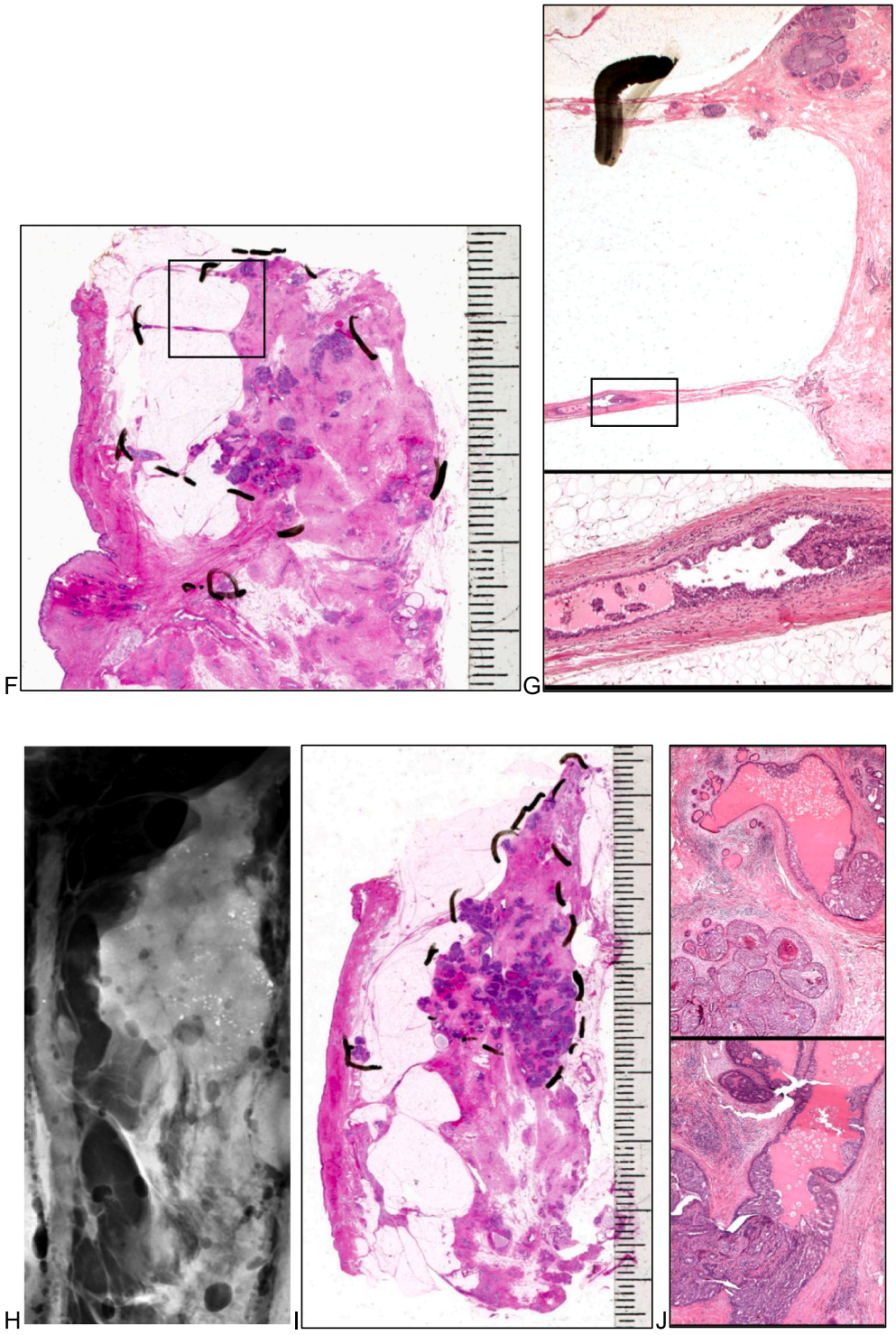


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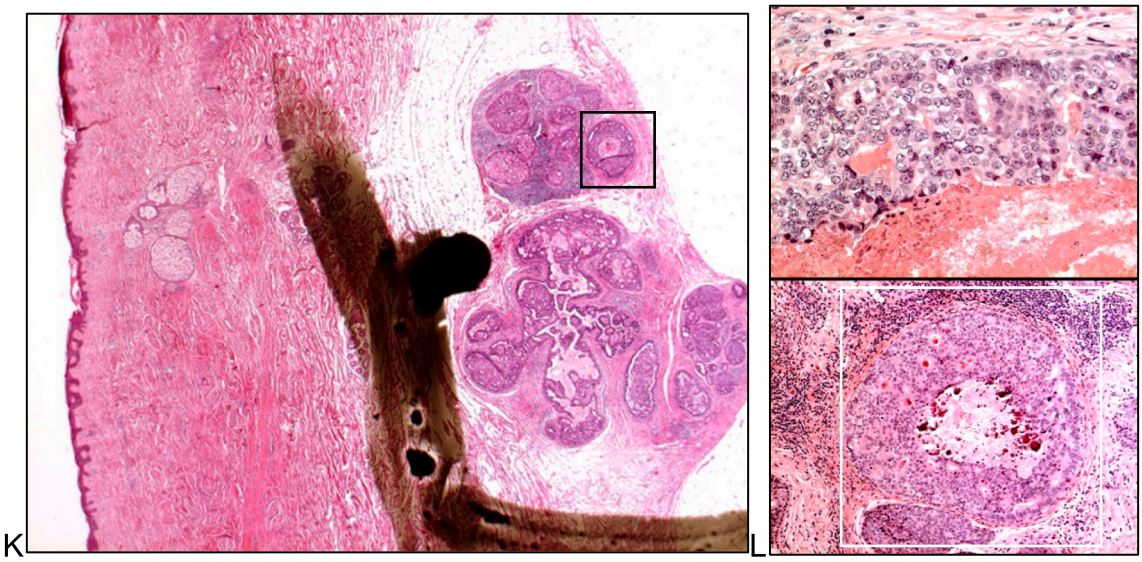


Fig. 7. (*continued*).

imaging biomarker, architectural distortion, indicates the presence of an extensive malignant process with a poor outcome. On the contrary, the immunohistochemical biomarkers deceptively indicate a disease with a very favourable long-term prognosis and may thus adversely influence management decisions [6].

Fig. 8 illustrates a diffusely infiltrating breast cancer, which we consider to have a mesenchymal hybrid cell origin (BCMO). This 53-year old woman presented with diffuse palpable thickening in her left breast in the interscreening interval.

5. Conclusions

Regular participation in mammography screening and the use of modern therapy have halved the number of breast cancer deaths, but the remaining breast cancer deaths are disproportionally concentrated among the multifocal and diffuse cancers. The introduction of breast conserving surgery has exposed the importance of determining for each patient the unifocal, multifocal or diffuse nature of breast cancer preoperatively using multimodality imaging, including breast MRI, to guide appropriate management. Postoperative image guided large section histopathology technique is equally essential to establish the full extent of the tumour [17]. In combination, this strategy provides an effective approach to treatment planning.

The integration of imaging biomarkers into breast cancer management reliably identifies the multifocal AABs and the two diffusely infiltrating breast cancer subgroups for the purpose of developing and implementing more effective management strategies. Documentation of the full extent of multifocal tumours, confirmation of the contiguous nature of diffusely invasive cancers, and a more comprehensive evaluation of surgical tissue margins are strategies providing a more robust evidence base for management decisions. Consensus decisions at pretreatment planning conferences are a golden opportunity to maximize benefits and minimize risks by avoiding the extremes of undertreatment and overtreatment as well as the extremes of underdiagnosis and overdiagnosis.

6. Summary of proposed strategies for improving the diagnostic workup of multifocal and diffusely infiltrating breast cancers

Although there has been considerable progress in breast cancer management, the following important advances have yet to become standards of routine breast cancer care:

- The use of imaging biomarkers to determine the site of tumour origin, a reliable predictor of long-term outcome.
- The use of breast MRI (alternatively abbreviated MRI or contrast-enhanced mammography) to assess the full extent of each breast cancer and to evaluate this assessment at the preoperative multidisciplinary meeting to help guide surgical management.
- Intraoperative communication with the surgeon of the results of the microfocus magnification specimen radiography and ultrasound examination of the surgical specimen in cases of mammographically occult lesions.
- Communication with the pathologist of the full imaging workup at the time of gross specimen examination and sectioning. This includes the findings on the mammograms, ultrasound, breast MRI and microfocus magnification radiograms of sliced breast specimens to assist in the determination of disease extent, multifocality and margin status. This communication eliminates an unnecessary, yet commonplace information gap between imager and pathologist.
- Comprehensive multidisciplinary postoperative evaluation, including thorough imaging-histopathological correlation and comprehensive evaluation of the surgical resection margin to provide a more reliable evaluation of the success of surgery and the need for further examinations, procedures and adjunctive therapy. This

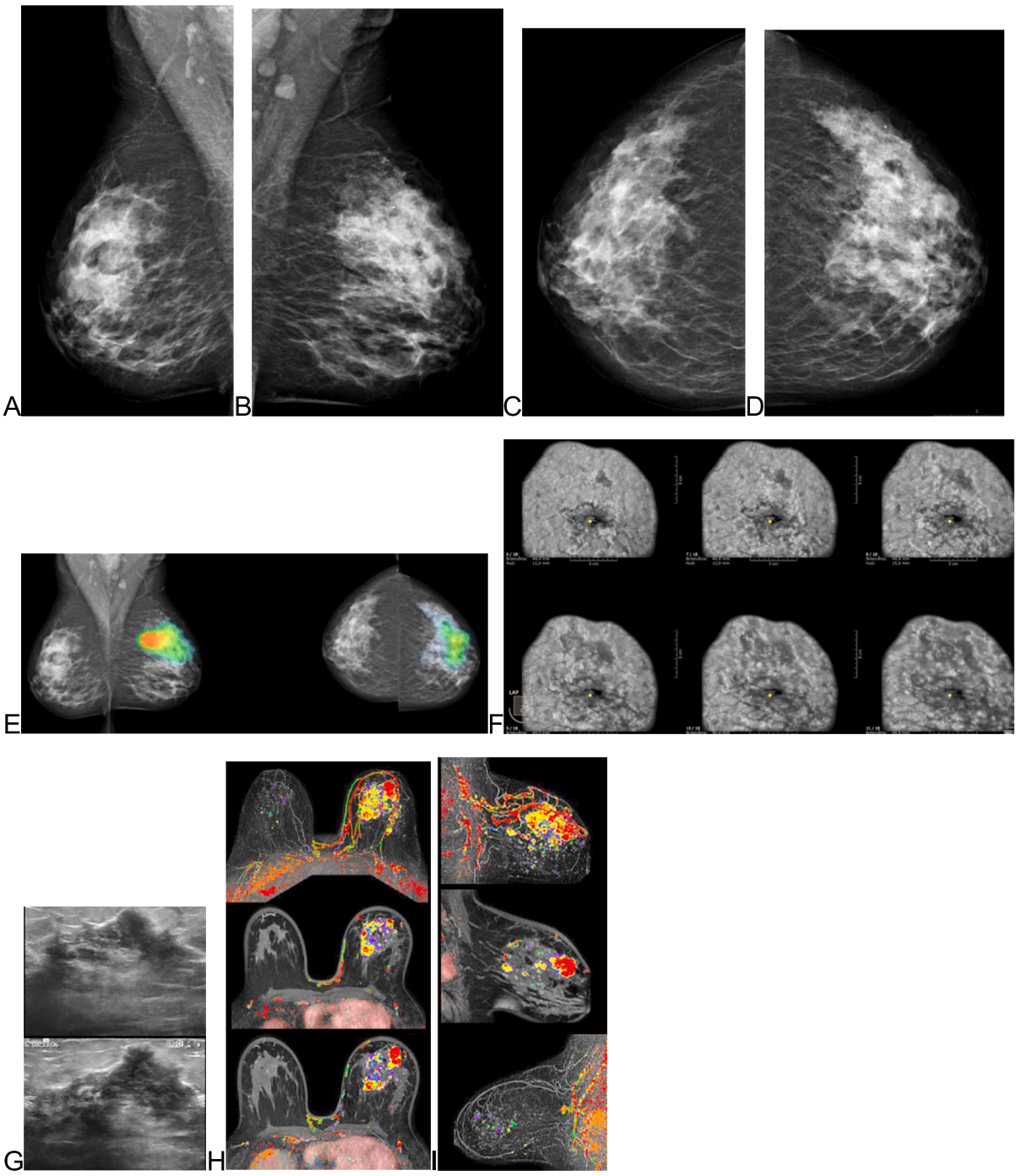
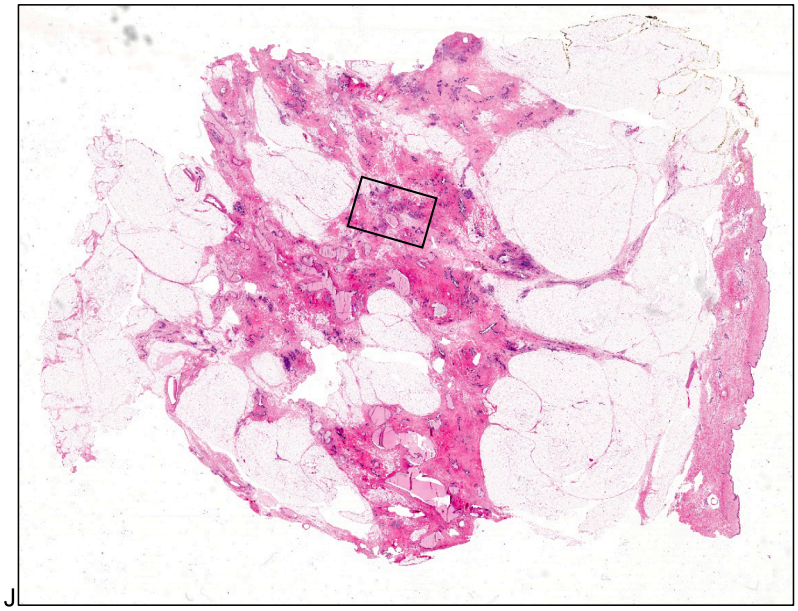
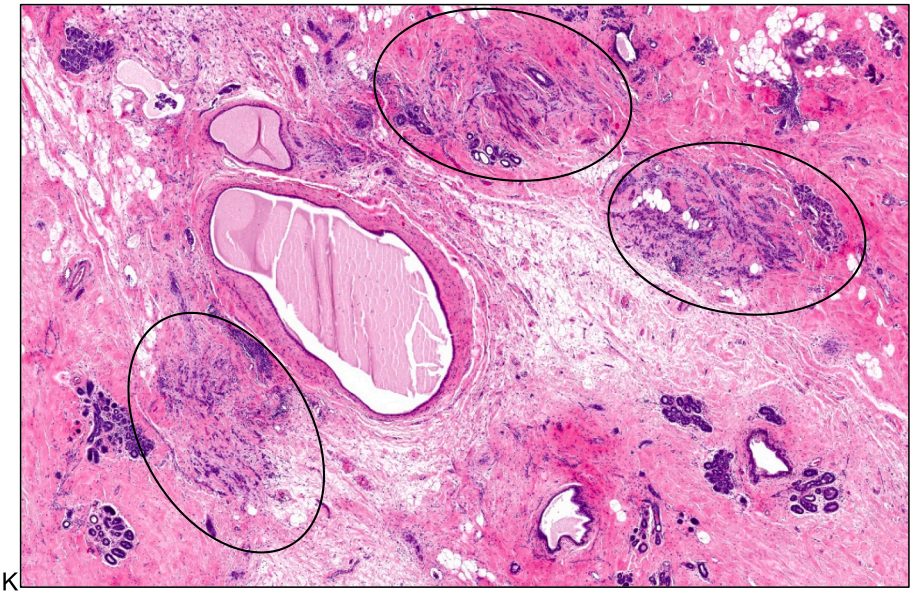


Fig. 8. Medio-lateral (A,B) and cranio-caudal (C,D) projections. Dense breasts (BI-RADS D) with no apparent tumor mass, microcalcifications or architectural distortion on the mammograms. There is a pathologic lymph node in the left axilla. Artificial intelligence (E) indicates the presence of a very extensive malignancy in the upper portion of the left breast. Automated breast ultrasound (F), hand-held ultrasound (G) and breast MRI (H,I) examinations confirm the presence of an extensive malignant lesion occupying most of the upper half of the left breast. The patient received preoperative neoadjuvant chemotherapy. Low and intermediate power large format thin section histopathology images (J,K) following mastectomy. Despite neoadjuvant chemotherapy, there are multiple viable, poorly differentiated cancer foci spread throughout the entire tissue slice, well demonstrated by the higher power, large format histopathology images (L,M).



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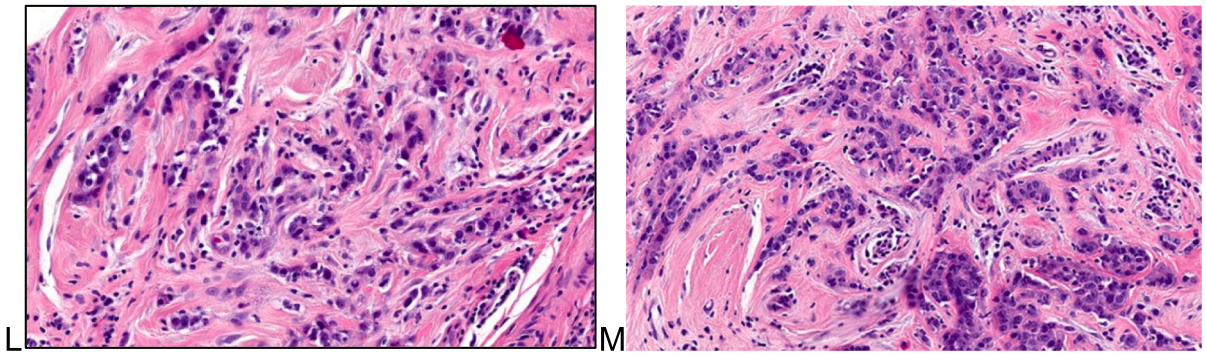


Fig. 8. (*continued*).

results in a rewarding learning environment combining presurgical and postsurgical imaging-pathology correlation [2,33,34].

- The postoperative report for every breast cancer case should not neglect essential features such as the imaging biomarkers and tumour growth patterns (unifocal, multifocal, diffuse).

Implementation of these advances and documentation of their impact upon management can serve as important quality control measures of the performance of the interdisciplinary breast team.

CRediT authorship contribution statement

László Tabár: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Peter B. Dean:** Supervision, Validation, Writing – original draft, Writing – review & editing. **F. Lee Tucker:** . **Amy Ming-Fang Yen:** . **Tony Hsiu-Hsi Chen:** . **Wendy Yi-Ying Wu:** Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. **András Vörös:** Investigation, Supervision, Validation, Writing – review & editing.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2023.110854.

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