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PICTORIAL ESSAY

Molecular Classification and Respective Radiological Phenotypes of Breast Cancers: A Pictorial Essay

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INTRODUCTION

According to the Centre for Health Protection, breast cancer is the most common cancer among females in Hong Kong.[1] In all, 4956 new cases of female breast cancer were diagnosed in Hong Kong and the crude incidence rate was 121.9 per 100,000 women in 2020.[1] Breast cancer is traditionally classified based on the clinicopathological analysis. In the past two decades, identification of distinct gene expression profiling in breast cancer has reshaped our understanding of breast cancer biology. Unravelling the genetic heterogeneity of breast cancer is fundamental to the development of personalised medicine, which improves clinical outcomes.

Full genomic analysis is costly and time-consuming, therefore not widely available in routine practice; the St Gallen International Expert Consensus panel has suggested the analysis of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) by semiquantitative immunohistochemistry (IHC) and the use of fluorescence in situ hybridisation for HER2 for equivocal IHC to define the four molecular subtypes of breast cancer (Figure 1).[2] IHC analysis may not always accurately reflect the true molecular subtypes of breast cancers. Discordance rates between IHC analysis and genetic expression profiling vary among different studies, but can be as high as 30%.[3]

The four intrinsic molecular subtypes of breast cancer include luminal A, luminal B, HER2-enriched, and basal-like (triple-negative). Each molecular subtype shows different demographics, treatment responses, preferential metastatic target organs, and prognoses. Importantly, distinctive radiological features of each molecular subtype have been identified (Table).[4-7]

This article aims to provide radiologists with a pictorial

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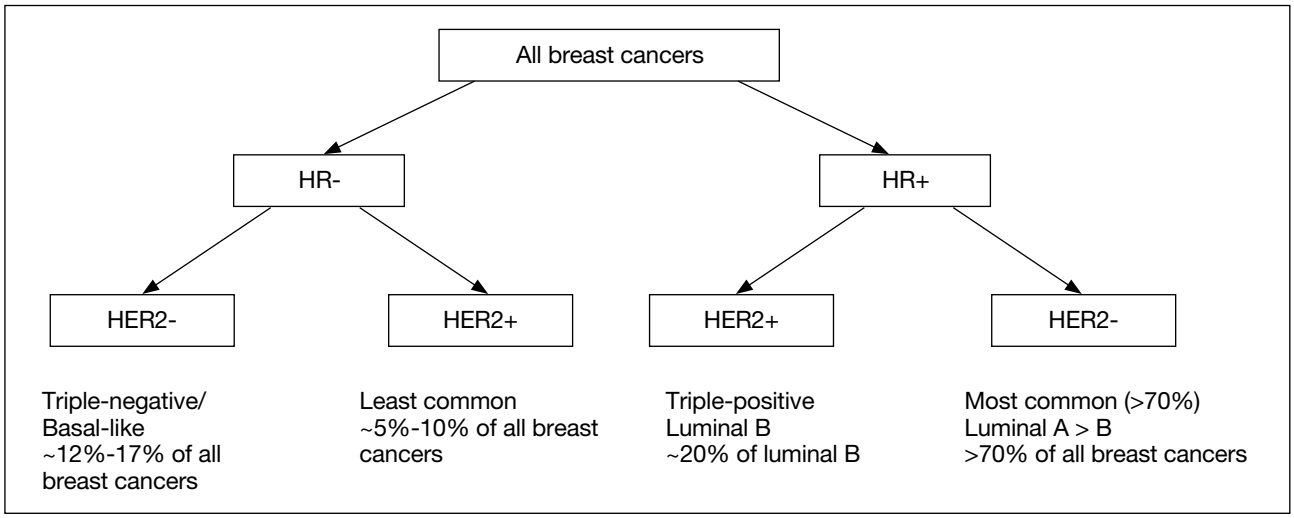

Figure 1. Simplified flowchart for molecular classification of breast cancer subtypes.
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Table. Summary of radiological phenotypes for different breast cancer molecular subtypes.[4-7]

Subtype and cancer grade	Molecular profile	Mammography	Ultrasonography	Magnetic resonance imaging
Luminal A, usually low grade	HR+*, HER2-, low Ki-67 level	Irregular mass with spiculated margin ± microcalcifications	Irregular mass with non-circumscribed margins and posterior acoustic shadowing	Irregular mass with spiculated margins
Luminal B, usually intermediate-to-high grade	ER+, PR-/low, high Ki-67 level, ± HER2+ (20% HER2+/80% HER2-)	Irregular mass with spiculated margins ± microcalcifications	Irregular mass with non-circumscribed margins and posterior acoustic shadowing	Multicentric and/or multifocal disease
HER2-enriched, usually intermediate-to-high grade	HR-*, HER2+	Indistinct mass with microcalcifications (branching or fine linear)	Non-mass lesion with non-circumscribed/indistinct margins	A washout or fast initial kinetics Multicentric and/or multifocal disease
Basal-like (triple-negative), high grade	HR-*, HER2-	Round mass with circumscribed margins Posterior in location No microcalcifications	Mass with relatively circumscribed margins Solid-cystic mass/necrotic tumour Posterior acoustic enhancement	Mass enhancement or rim enhancement with internal high T2 signal Peritumoral oedema

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; Ki-67 = antigen Ki-67; PR = progesterone receptor.
* Includes oestrogen receptor and progesterone receptor.

exhibit on imaging phenotypes of breast cancer molecular subtypes based on pathologically proven examples. It also provides an overview of molecular classification and clinical implications of each molecular subtype for the field of precision medicine.

LUMINAL SUBTYPE (LUMINAL A AND LUMINAL B)

Genetic Expression and Clinical Implications

Luminal subtype is defined by the presence of ER and PR expression.[4] Luminal subtype is divided into two distinct subgroups, namely luminal A and luminal B. Approximately 70% of breast cancers are luminal subtype breast cancers and they show a more favourable prognosis than hormone receptor–negative breast cancers.[5]

Luminal A subtypes are defined by expression of both ER and PR without amplification of the HER2/neu proto-oncogene. Patients with luminal A tumours have the best

prognosis among all molecular subtypes.[4-6] Luminal A tumours usually exhibit low histological grades with higher expression of hormone receptors (ERs and PRs) and lower proliferative activity, which can be assessed through Ki-67 expression, in which the antigen Ki-67 is a marker for cell proliferation (<14%).[4]

Luminal B subtypes also express ER and PR but they have a higher Ki-67 expression (≥14%).[4] Luminal B tumours are more often multifocal or multicentric and more likely to metastasise to regional nodes than luminal A tumours.[7] Patients with luminal B breast cancers often have a poorer prognosis compared to patients harbouring luminal A breast cancers.[5,7] Furthermore, 20% of luminal B tumours are HER2 positive by IHC analysis, referred to as the 'luminal B HER2+' subtype, which was shown to be associated with a poorer prognosis and lower 10-year breast cancer–specific survival rate among the luminal subtypes.[7]

The hormone receptor status is predictive of response to hormone therapy, the mainstay of treatment for patients with luminal breast cancers.[3,6]

Imaging Characteristics

Luminal tumours typically demonstrate suspicious mammographic features of breast cancer, namely an irregular mass with spiculated or microlobulated margins or a mass with suspicious microcalcifications (Figures 2 and 3).[6] Associated architectural distortion

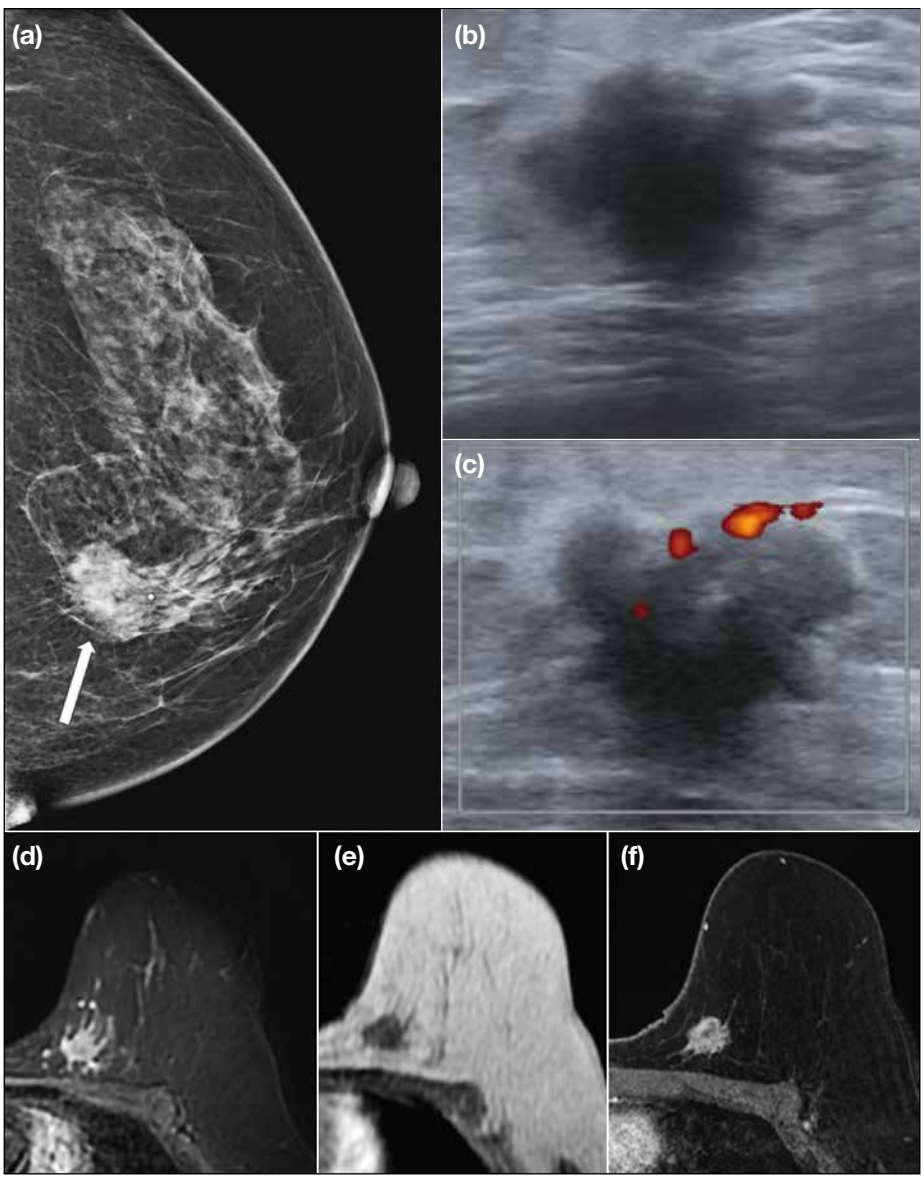

Figure 2. A 59-year-old woman with luminal A breast cancer (oestrogen receptor 95%, progesterone receptor 95%, c-*erb*B2 0+, and Ki-67 ~10%). (a) Craniocaudal mammographic view showing an irregular high-density mass (arrow) with spiculated margins in upper inner left breast. (b) Greyscale and (c) colour Doppler images showing an irregular mass with spiculated margins and intrinsic vascularity. (d) Axial fat-suppressed T2-weighted magnetic resonance (MR) image showing an irregular hyperintense mass with spiculated margins. (e) Axial non-contrast T1-weighted and (f) contrast-enhanced T1-weighted fat-saturated MR images showing heterogenous enhancement in the corresponding mass.

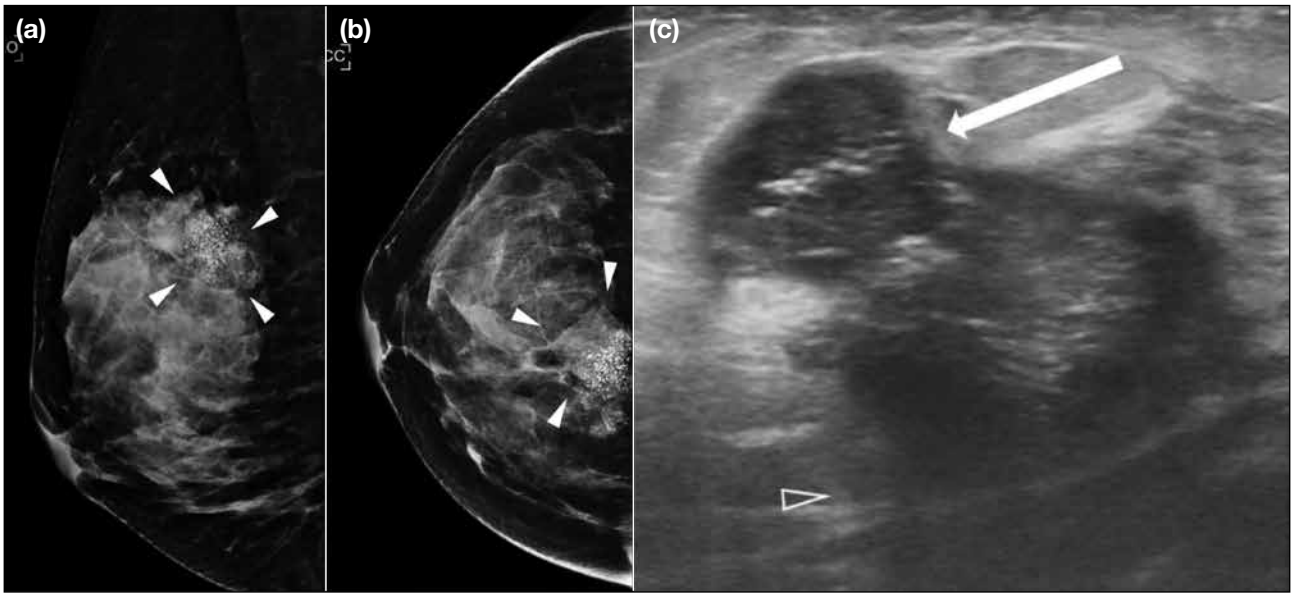

Figure 3. A 41-year-old woman with luminal B breast cancer (oestrogen receptor 70%, progesterone receptor 30%, c-*erb*B2 0+, and Ki-67 ~30%). (a) Mediolateral-oblique and (b) craniocaudal mammographic views showing an equal-density irregular mass with partially obscured margins and associated pleomorphic calcifications (arrowheads) in the upper inner right breast, which is a common presentation for luminal breast cancer. (c) Ultrasound image showing an irregular hypoechoic mass with angular margins and posterior acoustic shadowing (open arrowhead); microcalcifications (arrow) can be appreciated within the mass.

is more commonly observed in luminal A tumours than in luminal B tumours. The sonographic appearance of luminal tumours is typically an irregular mass with posterior acoustic shadowing (Figures 2 and 3).[6] On magnetic resonance imaging (MRI), luminal tumours most commonly present as an enhancing irregular mass with spiculated margins (Figure 2).[8]

Luminal B tumours are more frequently associated with axillary nodal metastases at the time of diagnosis than luminal A tumours. Luminal B tumours more often present with multifocal or multicentric disease on MRI.[3] The 'luminal B HER2+' subtype has been reported to be more likely to involve axillary lymph nodes and to present with multifocal or multicentric disease on MRI (Figure 4).[3]

Distant metastasis in luminal breast cancers shows a greater propensity to involve the skeletal system compared to other breast cancer subtypes (Figure 5).[9,10]

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2–ENRICHED SUBTYPE

Genetic Expression and Clinical Implications

HER2-positive cancers are defined by overexpression of the c-*erb*B2 (HER2/neu) gene, which encodes the epidermal growth factor receptor type 2.[6] Of all HER2-positive tumours, 60% are HER2-enriched, characterised by HER2 positivity and ER and PR negativity.[6] Being a proto-oncogene, amplification of c-*erb*B2 results in increased cellular aggressiveness and faster growth.

HER2-enriched breast cancers are generally intermediate-to-high-grade tumours with an aggressive course, worse survival rate, and higher recurrence rate compared to luminal breast cancers.[5]

Fortunately, HER2-directed therapy has shown success in improving clinical outcomes, and trastuzumab therapy is a widely used and effective anti-HER2 agent.

Imaging Characteristics

HER2-enriched tumours most commonly present as a mass associated with microcalcifications or as suspicious microcalcifications alone on mammography (Figure 6).[6] The margins of HER2-enriched tumours are usually spiculated. Sonographically, HER2-enriched tumours are usually iso- to hypoechoic with indistinct margins and a high degree of vascularity (Figure 6).[6] On MRI, a round mass with spiculated margins and non-mass enhancement are the most frequent patterns in HER2-enriched subtype.[6,8] HER2-enriched tumours are often multifocal and/or multicentric on MRI and are frequently associated with ductal carcinoma in situ (Figure 7).[6,8]

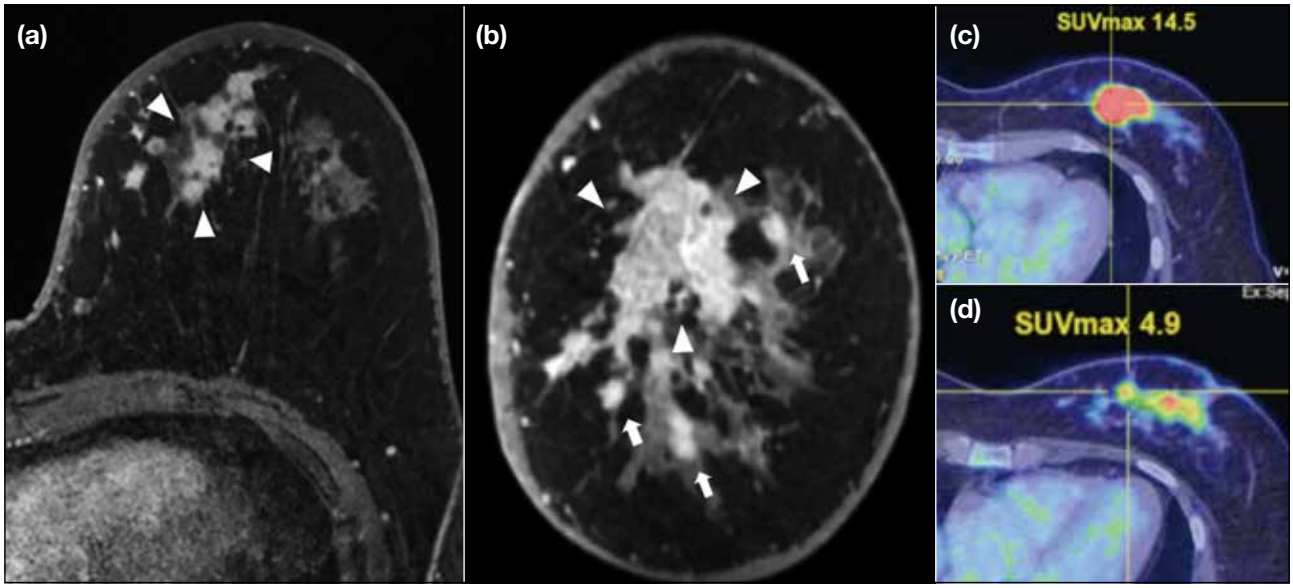

Figure 4. A 55-year-old woman with multicentric luminal B human epidermal growth factor receptor 2 + breast cancer (oestrogen receptor 90%, progesterone receptor 60%, c-*erb*B2 2+, and Ki-67 ~30%). (a) Axial and (b) coronal contrast-enhanced T1-weighted magnetic resonance images showing an irregular enhancing mass with spiculated margins in the upper inner quadrant of the left breast (arrowheads) with multiple smaller enhancing foci (arrows in [b]) in the lower inner and upper outer quadrants of the left breast, consistent with multicentric disease. (c and d) Corresponding fusion images of positron emission tomography/computed tomography depict a lobulated hypermetabolic mass in the upper inner quadrant (maximum standardised uptake value [SUV_{max}] = 14.5) and multiple small hypermetabolic foci in the lower inner quadrant (SUV_{max} = 4.9), again consistent with multicentric disease.

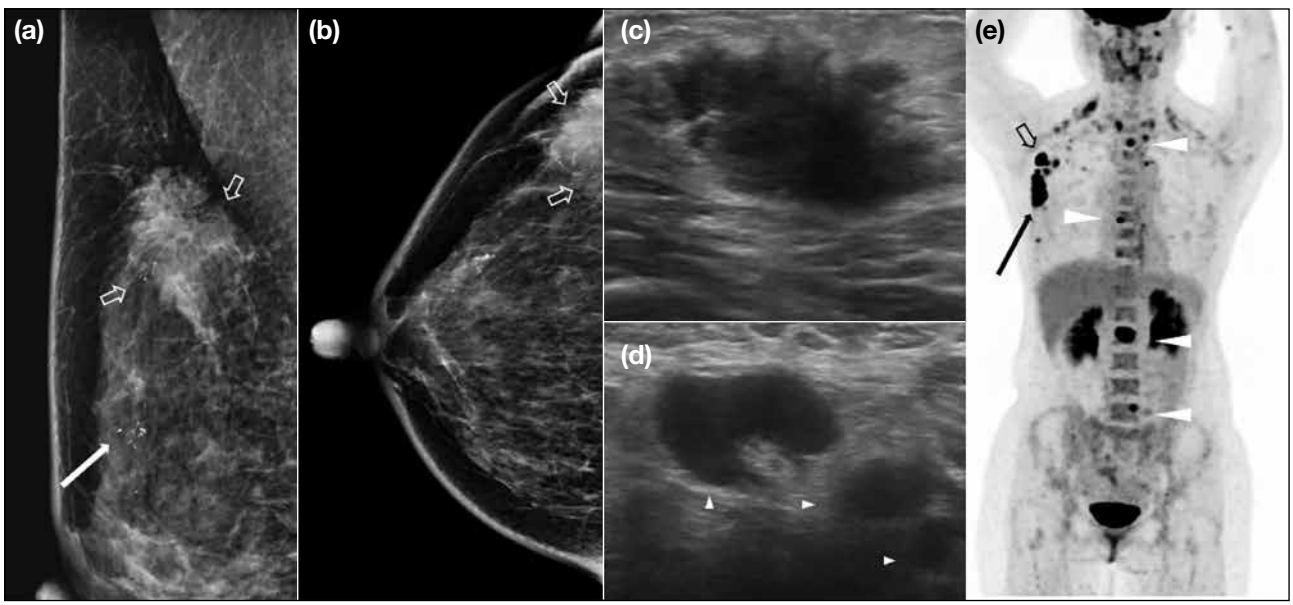

Figure 5. A 43-year-old woman with luminal B breast cancer and multiple bone metastases (oestrogen receptor 60%, progesterone receptor 30%, c-*erb*B2 0+, and Ki-67 ~20%). (a) Mediolateral-oblique and (b) craniocaudal mammographic images showing an irregular high-density mass with spiculated margins in the upper outer right breast (open arrows), with pleomorphic microcalcifications (arrow in [a]). (c) Ultrasound image of the mass shows that it is irregular and hypoechoic with spiculated margins. (d) Ultrasound of the right axilla shows multiple enlarged nodes (arrowheads) with eccentric cortical thickening and loss of fatty hilum suggestive of nodal metastases. (e) Maximal intensity projection image of whole-body positron emission tomography showing a hypermetabolic primary tumour in the upper outer quadrant of the right breast (arrow) with axillary node involvement (open arrow) and multiple sites of bone metastases in the spine (arrowheads).

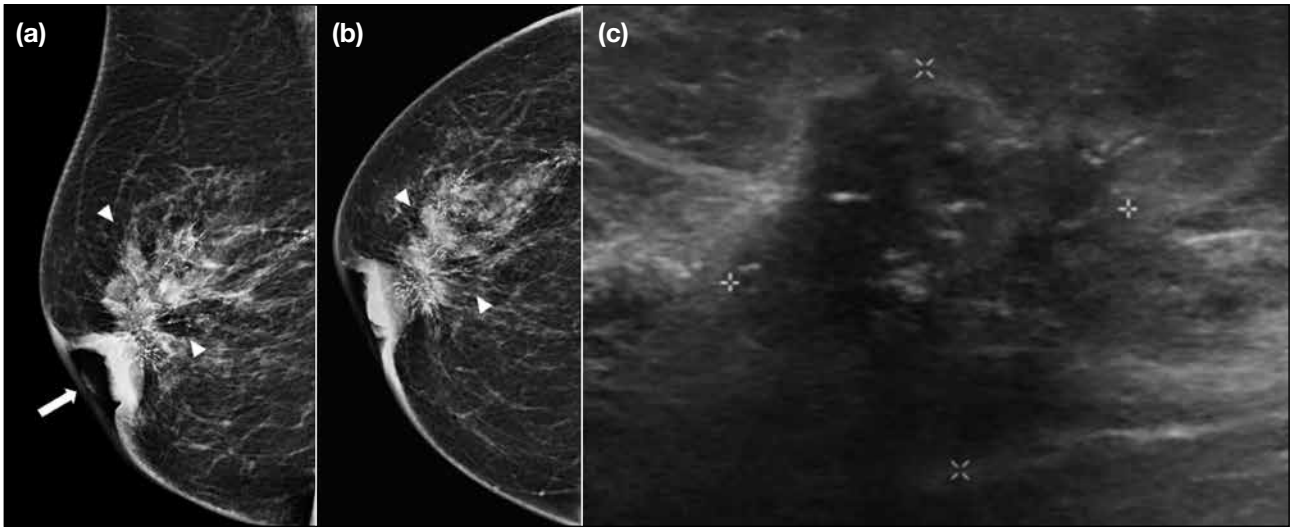

Figure 6. An 84-year-old woman with human epidermal growth factor receptor 2–enriched breast cancer (oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 3+, and Ki-67 ~35%). (a) Mediolateral-oblique and (b) craniocaudal mammographic views of the right breast showing an irregular high-density mass in the retroareolar region, with spiculated margins and associated fine-linear branching microcalcifications in a segmental distribution (arrowheads). Marked nipple retraction (arrow in [a]) is suggestive of nipple involvement. (c) Ultrasound image showing an irregular hypoechoic mass with indistinct margins and posterior acoustic shadowing.

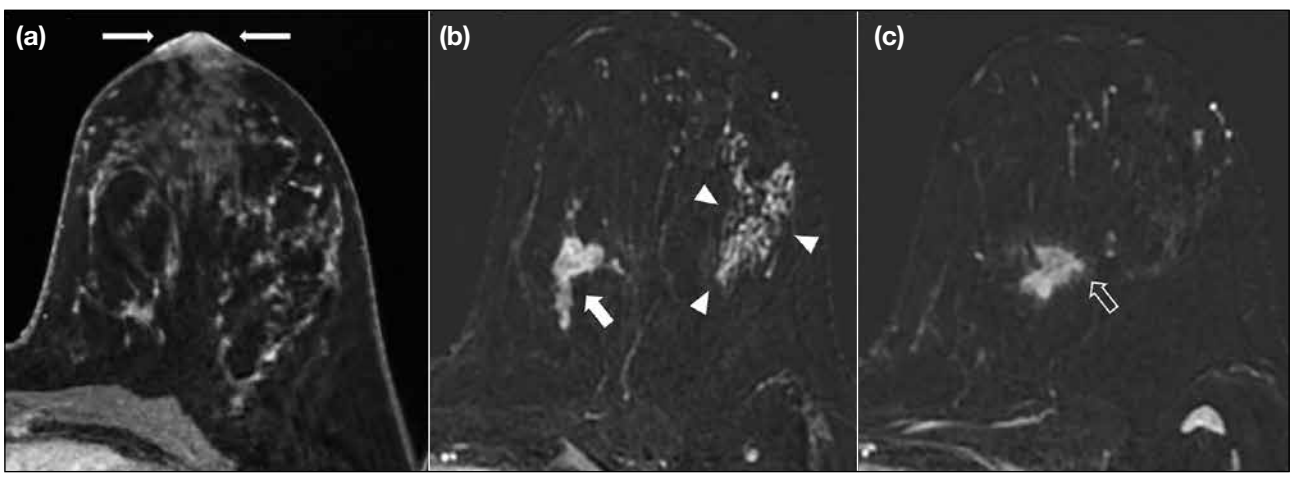

Figure 7. A 42-year-old woman presented with left mammary Paget's disease and was subsequently found to have multicentric human epidermal growth factor receptor 2 (HER2)–enriched breast cancer (oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 3+, and Ki-67 ~20%) and ductal carcinoma in situ (DCIS). (a) Axial contrast-enhanced T1-weighted subtraction magnetic resonance (MR) image depicts abnormal enhancement involving the left nipple and periareolar region (arrows) in keeping with Paget's disease. (b and c) Axial contrast-enhanced T1-weighted subtraction MR images showing multicentric disease with two irregular and spiculated enhancing masses in the left breast (arrow in [b] and open arrow in [c]), both of which were histologically proven to be HER2-enriched breast cancer. Segmental non-mass enhancement in the outer aspect of the left breast (arrowheads in [b]) corresponds to the coexisting DCIS.

Distant metastases in HER2-enriched breast cancers show a propensity to involve the brain (Figure 8).[9]

The HER2-enriched subtype is found to be the most frequent breast cancer molecular subtype associated with mammary Paget's disease (Figure 7).[11]

BASAL-LIKE SUBTYPE (TRIPLE-NEGATIVE)

Genetic Expression and Clinical Implications

Triple-negative breast cancer (TNBC) is defined by lacking expression of ER, PR and HER2. The term 'triple-negative' is often used as a synonym for the

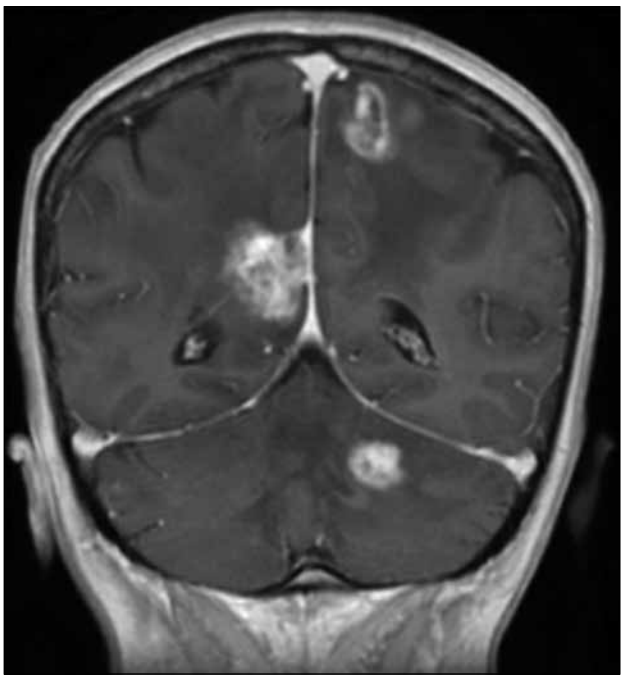

Figure 8. A 45-year-old woman with stage 4 human epidermal growth factor receptor 2–enriched breast cancer (oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 3+, and Ki-67 ~40%). Coronal contrast-enhanced T1-weighted magnetic resonance image shows multiple enhancing brain metastases.

'basal-like' subtype because 86% of TNBC are the basal-like subtype.[6] TNBC accounts for 12% to 17% of all breast cancers,[12,13] preferentially affecting young women of African descent and carriers of germline breast cancer susceptibility gene 1 (BRCA1) and partner and localiser of BRCA2 (PALB2) mutations.[13]

TNBC has a tendency to develop early metastases to lung and brain, leading to rapid progression.[10,12] The time from distant recurrence to death is much shorter in triple-negative tumours than in other subtypes due to the relatively high mortality associated with visceral soft tissue metastases as compared to bone metastases in the luminal subtypes.[10] When compared with other breast cancer subtypes, patients with TNBC also experience a higher frequency (34% vs. 20%) and earlier onset (2.6 vs. 5.0 years after diagnosis) of distant recurrence.[10] Recurrences most commonly occur 1 to 4 years after diagnosis and are rare beyond 8 years, in contrast to the constant risk throughout the follow-up period in ER-positive tumours.[10] Due to the aggressive tumour biology and limited targeted therapy, patients harbouring TNBCs show poorer prognosis than patients with hormone receptor–positive tumours.[5,10]

TNBC has been shown to have greater sensitivity to neoadjuvant chemotherapy with a better pathological complete response than luminal and HER2 subtypes.[12] Conventional adjuvant chemotherapy using anthracycline/taxane-based regimens remains the standard of care for patients with TNBCs despite the identification of several promising agents, such as platinum.[12]

Imaging Characteristics

TNBC frequently presents as a palpable mass and often lacks the classical suspicious mammographic features, namely irregular mass, spiculated margins, and suspicious microcalcifications. Unifocal disease, circumscribed mass despite large size, necrotic mass with posterior enhancement on ultrasound, and absent calcifications on mammography are the imaging phenotype of TNBC (Figures 9 and 10).[14] TNBCs also show tendency towards a posterior or pre-pectoral location compared to other breast cancer subtypes (Figure 9).[15] Due to the apparent benign features on mammography and ultrasonography, TNBC may be mistaken as a fibroadenoma or complicated cyst (Figure 9). Besides the conventional techniques of mammography and ultrasound, dynamic contrast-enhanced MRI may serve as a useful adjunct to distinguish them by analysis of their enhancement patterns and respective kinetic curves (Figure 11). MRI breast kinetic curves, categorised into type I (progressive), type II (plateau), and type III (washout), offer distinguishing patterns in malignancy suspicion. Progressive curves, which demonstrate continuous enhancement over time, typically denote benignity. Plateau curves, characterised by initial enhancement followed by a plateau phase, raise concerns for malignancy. Washout curves, characterised by an initial uptake and subsequent washout, strongly imply malignancy.

TNBC has been shown to have a higher tumour roundness score compared with the other subtypes, reflecting a more biologically aggressive tumour type (Figures 9 and 10).[14] In contrast to luminal and HER2-enriched subtypes, there is no linear correlation between tumour size and the likelihood of lymph node involvement (Figure 12).[10,16]

Typical MRI findings in TNBC are mass enhancement and rim enhancement, which are related to tumour necrosis in these high-grade and fast-growing tumours.[8,14] The presence of peritumoral oedema was found to be the only significant variable associated with worse recurrence-free survival in patients with TNBC.[17]

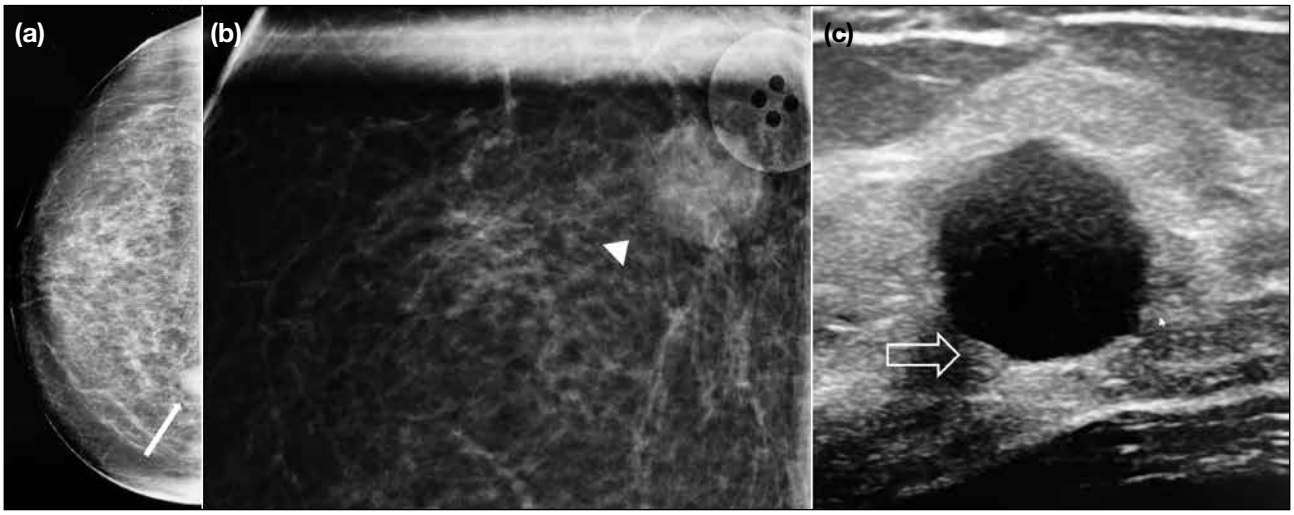

Figure 9. A 55-year-old woman with triple-negative breast cancer (TNBC) [oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 0+, and Ki-67 ~40%]. (a) Craniocaudal mammographic view showing a partially included high-density, round mass (arrow) at posterior one-third of the inner right breast. (b) Coned magnified mediolateral mammographic view showing a high-density round mass with well-circumscribed margins (arrowhead). (c) Ultrasound showing a hypoechoic round mass with relatively circumscribed margins and posterior acoustic enhancement (open arrow). These apparently benign imaging features of TNBC could mimic a fibroadenoma or complicated cyst.

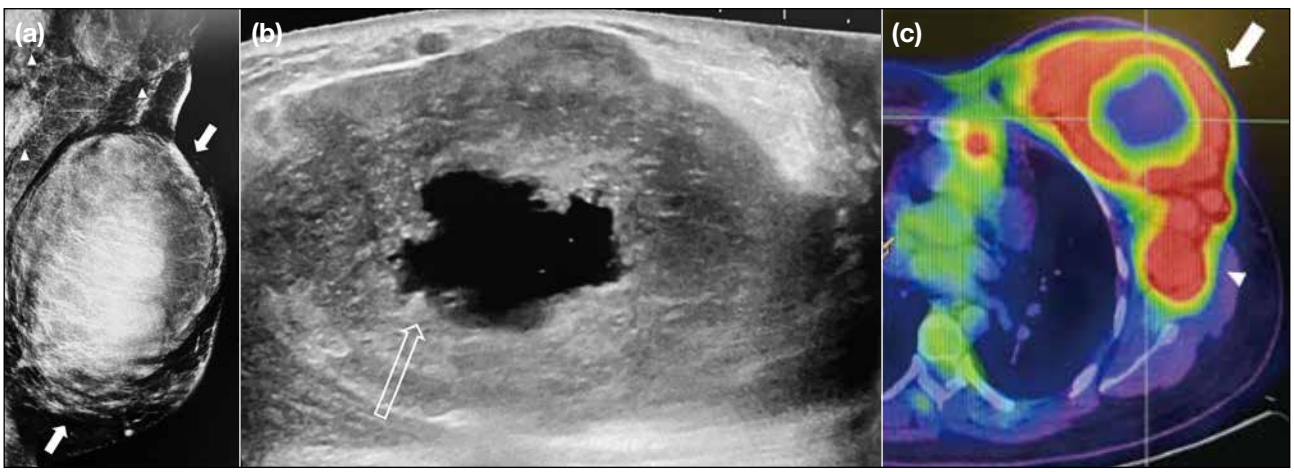

Figure 10. A 32-year-old woman with triple-negative breast cancer (oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 0+, and Ki-67 >80%). (a) Mediolateral-oblique mammographic view showing a large, oval high-density mass (arrows) with relatively circumscribed margins occupying almost the entire left breast accompanied by bulky left axillary lymphadenopathy (arrowheads). (b) Ultrasound showing a lobulated necrotic mass with a central cystic area suggestive of tumour necrosis (open arrow). (c) Positron emission tomography/computed tomography showing hypermetabolic uptake in the left breast necrotic tumour (arrow; maximum standardised uptake value [SUV_{max}] = 19.2) and left axillary lymphadenopathy (arrowhead; SUV_{max} = 14.2).

MRI is the most sensitive imaging modality in the early prediction of neoadjuvant chemotherapy response and pathological complete response in patients harbouring TNBCs.[14] Most of the studies have shown that TNBCs are relatively chemosensitive compared to other subtypes. Placement of a marker clip within the TNBC prior to neoadjuvant chemotherapy allows precise localisation of the tumour for subsequent operation (Figures 13 and 14).

CONCLUSION

Knowledge of molecular classification of breast cancers allows better understanding of the clinical behaviour and prognosis of the different breast cancer subtypes, thus facilitating implementation of individualised therapies.

Precision medicine is the emerging approach for individualising patient treatment, which is the standard

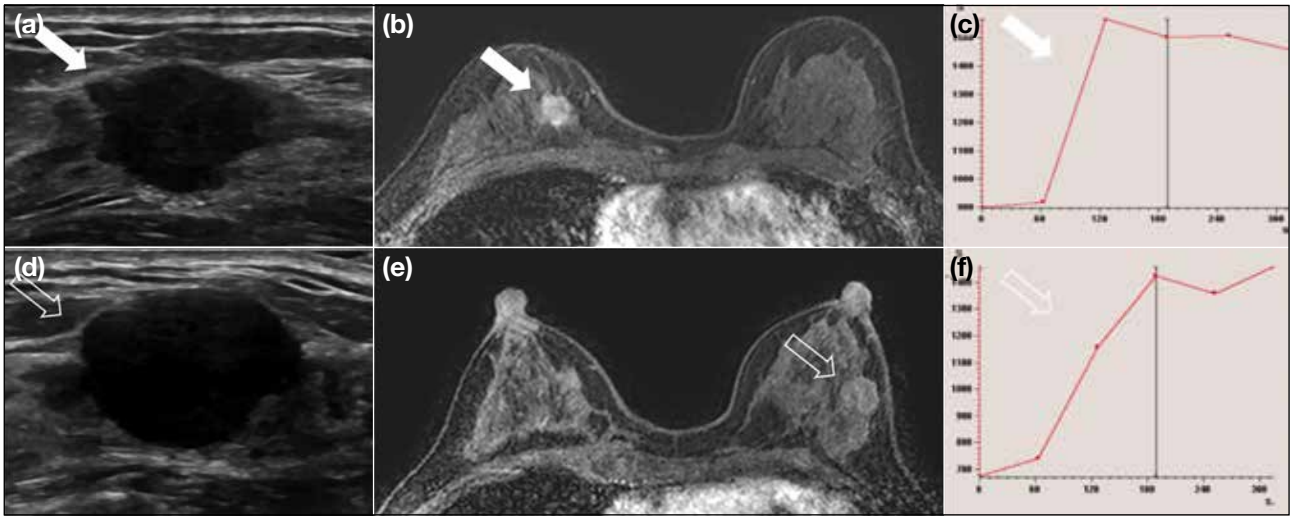

Figure 11. A 56-year-old woman with triple-negative right breast cancer (TNBC) [oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 1+/confirmed negative by fluorescence in situ hybridisation, and Ki-67 <10%] in the background of multiple fibroadenomas. (a-c) Biopsy-proven TNBC is found in the right breast (arrows). Ultrasound images show an irregular mass with angular margin in the right breast, with corresponding enhancement and a type III kinetic curve in dynamic contrast enhancement magnetic resonance imaging (MRI), which suggests malignancy. (d-f) Biopsy-proven fibroadenoma in the left breast (open arrows). Ultrasound images show a circumscribed mass in the left breast with corresponding enhancement and a type I kinetic curve in dynamic contrast enhancement MRI, which suggests benignity.

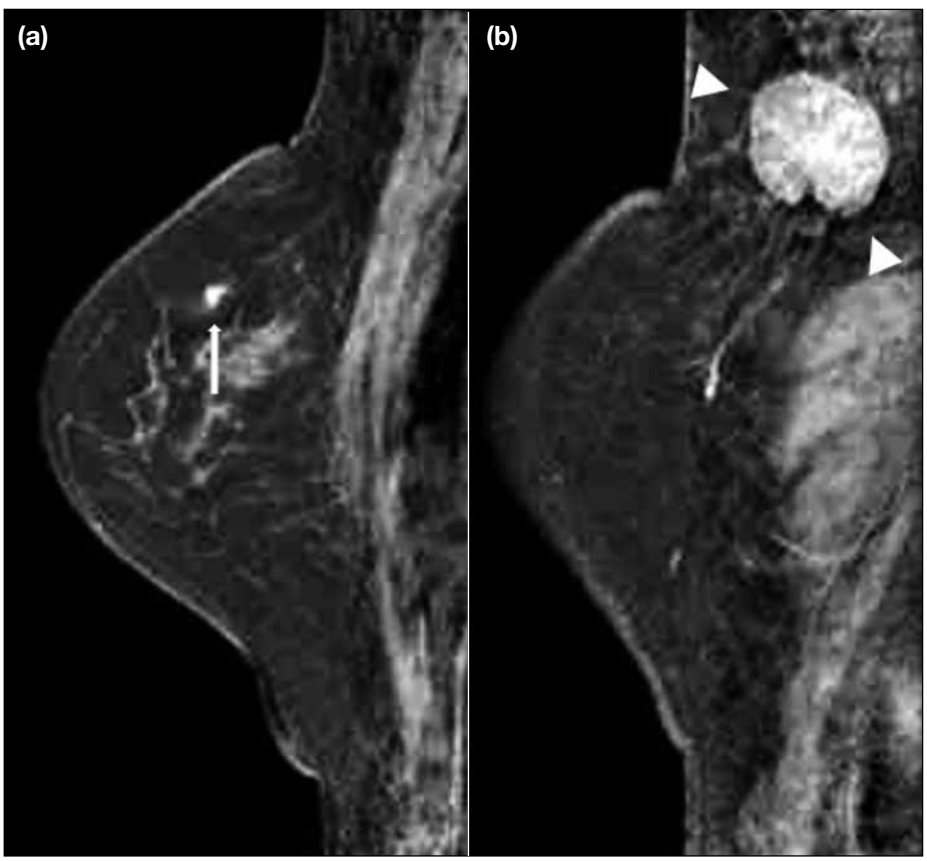

Figure 12. A 57-year-old woman with triple-negative breast cancer (TNBC) and a large axillary nodal metastasis (oestrogen receptor <1%, progesterone receptor <1%, and c-*erb*B2 0+). Sagittal contrast-enhanced T1-weighted magnetic resonance images showing (a) a small (0.5 cm) enhancing focus (arrow) in the upper right breast and (b) a large round, enhancing node (arrowheads) in the ipsilateral axilla, demonstrating non-linear correlation between the primary tumour size and the likelihood of lymph node involvement, a typical feature for TNBC.

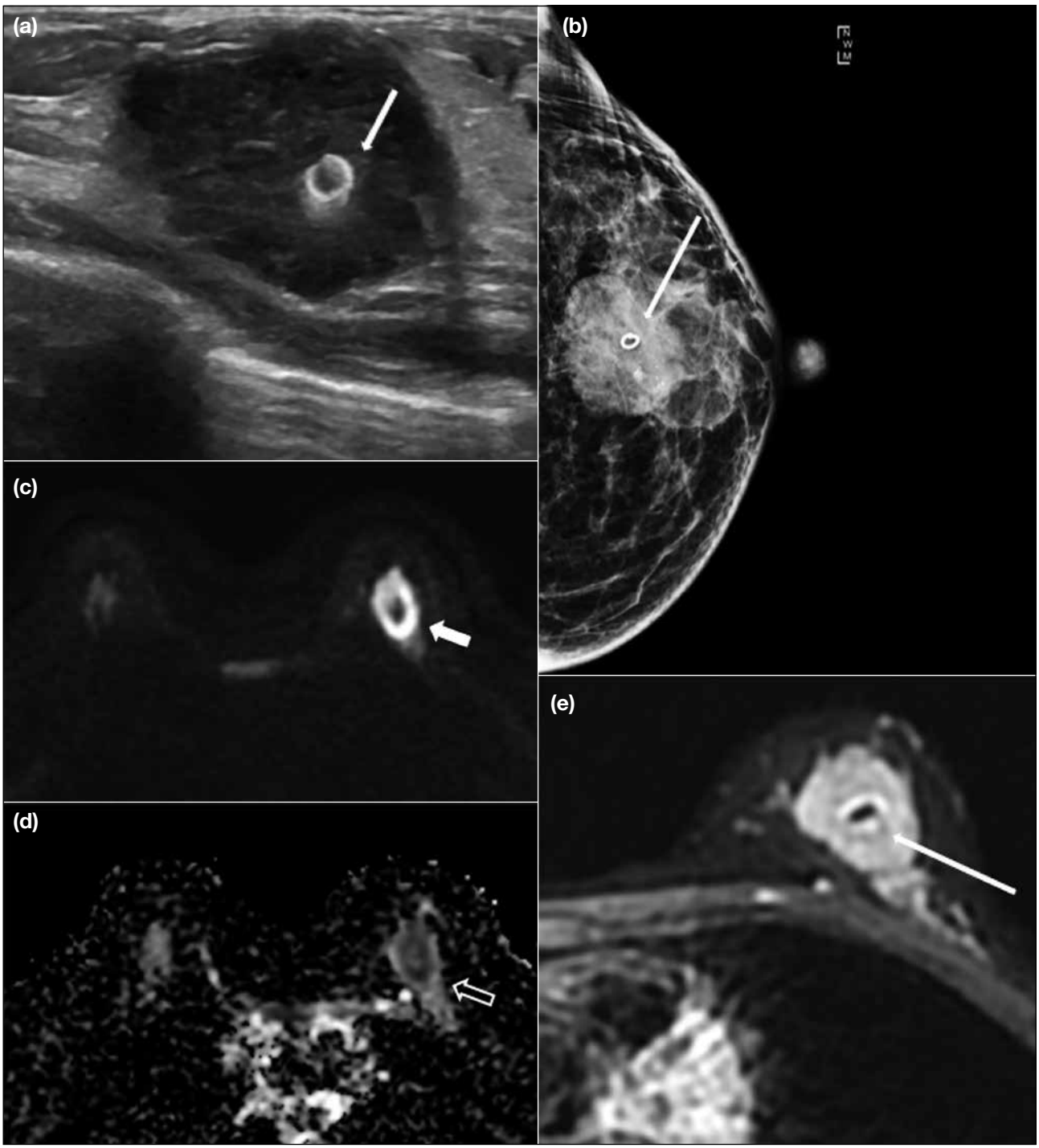

Figure 13. A 51-year-old woman with triple-negative breast cancer (TNBC) in the left breast [oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 0+, and Ki-67 ~95%] underwent ultrasound-guided marker insertion before neoadjuvant chemotherapy. (a) Ultrasound-guided insertion of marker (arrow) was performed via a 17-G needle. (b) Craniocaudal mammographic image demonstrates the correct placement of marker (arrow) within the biopsy-proven TNBC. (c) Axial diffusion-weighted image shows significant restriction of diffusion (arrow) in the tumour. (d) Corresponding apparent diffusion coefficient (ADC) image showing decreased ADC, as evidenced by the dark signal (open arrow) in the region of restricted diffusion. (e) Axial contrast-enhanced T1-weighted magnetic resonance image shows a signal void (arrow) within the enhancing breast mass, corresponding to the marker.

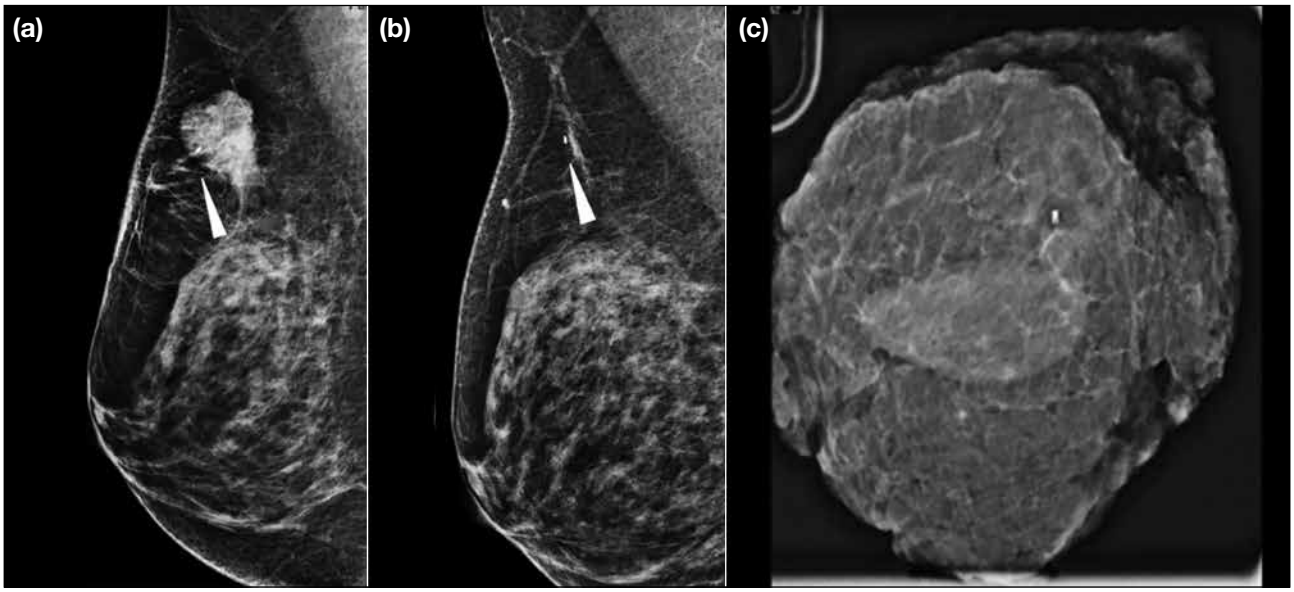

Figure 14. A 58-year-old woman with triple-negative breast cancer (TNBC) [oestrogen receptor <1%, progesterone receptor <1%, c-*erb*B2 0+, and Ki-67 ~65%] with complete radiological response to neoadjuvant chemotherapy. (a) Mediolateral-oblique mammographic image showing the placement of biopsy marker (arrowhead) within the biopsy-proven TNBC in the right breast. (b) Mediolateral-oblique mammographic image following neoadjuvant chemotherapy showing the marker (arrowhead) with complete resolution of the mass. (c) Radiograph of the lumpectomy specimen confirms the marker in situ with sufficient surgical margins.

of care for breast cancer management in the current era. The role of radiologists is no longer limited to establishing the diagnosis, staging, and surveillance of breast cancers. They play a vital role in guiding the investigation options based on the specific biology of breast cancer, assessment of neoadjuvant treatment response, and facilitating clinicians in optimising individualised patient care. Thorough understanding of breast cancer molecular subtypes is one of the biggest steppingstones amongst breast radiologists to participate in precision medicine practice.

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