The Role of Imaging in Young Breast Cancer

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Learning objectives

• To review the epidemiology, risk factors and histopathological features specific to breast cancer in women under 40 years.

• To review the imaging features of breast cancer in young women based on a series of 75 patients.

• To highlight the role of MRI in diagnosis and monitoring response to neoadjuvant chemotherapy.

• To emphasise the importance of triple assessment including biopsy to secure a histological diagnosis.
Background

Epidemiology

Breast cancer is the second most commonly diagnosed cancer in young women. In the UK, approximately 2,000 cases are diagnosed in women under the age of 40 every year\(^1\). The 5-year survival rate in women under 40 is worse than in women aged 40 to 69\(^2\) with a higher overall recurrence rate and a greater risk for developing distant metastases\(^3\). A recent study demonstrated that in patients aged <35 years, the risk of death rose by 5% for every 1-year reduction in age at diagnosis\(^4\). The low suspicion of malignancy in young women due to the lower prevalence of cancer often leads to delays in diagnosis. This highlights the importance of triple assessment including clinical evaluation, imaging and core biopsy to secure a definitive histological diagnosis.

Risk Factors

Breast cancer at an early age tends to be associated with genetic mutations, in particular BRCA1 and BRCA2. Women carrying these mutations have a lifetime risk of breast cancer of 60 to 80%\(^5\). Germline mutations in less common genes include TP53 and CHEK2 gene that are associated with Li-Fraumeni syndrome, PTEN gene associated with Cowden syndrome, STK11/LKB1 gene associated with Peutz-Jeghers syndrome, ATM gene associated with ataxia telangiectasia and CDH-1 gene in hereditary diffuse gastric cancer\(^6\). Non-genetic risk factors include breast tissue density, previous breast disease, radiation exposure and lifestyle factors such as weight, exercise and alcohol consumption\(^7\).

Histopathological Features

Breast tumours in young women are more likely to be high grade, poorly differentiated, hormone receptor negative and demonstrate lymphovascular invasion\(^8\). In particular, patients with BRCA1 associated breast carcinomas usually demonstrate a basal-like phenotype, which is associated with poor clinical outcomes. This is likely due to the subtype’s high proliferative capacity and the lack of directed therapies as basal-like tumours are typically triple negative ie. negative for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2).
Imaging findings OR Procedure details

Younger women have higher breast parenchymal density making it difficult to differentiate between tumour and normal breast tissue at mammography. Ultrasound imaging is more sensitive than mammography in evaluating breast masses in young women. However, the images have to be interpreted with caution, as cancers in young women can appear well-circumscribed, mimicking benign disease and core biopsy is important to secure a histological diagnosis.

Breast MRI adds valuable information in the assessment of young women with palpable breast masses that are histologically proven to be malignant following clinical core biopsy, but are occult on standard imaging techniques including mammography and ultrasound. MRI more accurately delineates tumour extent with the demonstration of multifocal, multicentric and contralateral disease that will influence surgical planning.

Due to the more aggressive tumour profile seen in young women, neoadjuvant chemotherapy plays an important role in the treatment pathway. Dynamic contrast-enhanced MRI allows visualisation of both morphologic and functional properties of the tumour and is a valuable tool for monitoring response to neoadjuvant therapy. Early identification of responders and non-responders to chemotherapy helps to tailor individualised treatment pathways and reduce unnecessary toxicity from ineffective regimes.

Case study 1

Clinical presentation: 36 year old presenting with a clinically benign right breast lump at the 10 o'clock position.

Imaging features:

- Mammogram on page 9 showed moderate density fibroglandular breast tissue but no focal abnormality (R1).
- Targeted ultrasound on page 9 of the right breast showed a 16mm poorly defined irregular hypoechoic solid mass with posterior acoustic shadowing, consistent with malignancy (U5). Ultrasound-guided core biopsy revealed an invasive lobular carcinoma.
- Breast MRI was performed to delineate tumour extent as mammographically occult and assess for multicentric and contralateral
disease in view of the lobular phenotype. MRI confirmed a unifocal irregular solid tumour with a type 5 malignant tumour activity curve.

**Surgical histology:** Right wide local excision confirmed a grade 2 invasive lobular carcinoma measuring 13mm, with no nodal metastasis.

**Teaching points:**

- Mammography is less sensitive in young females with dense breast tissue.
- Clinico-radiological discordance with a clinically benign lump and a malignant mass on ultrasonography, requires core biopsy for histological diagnosis.

**Case study 2**

**Clinical presentation:** 39 year old presenting with a clinically benign lump in the upper outer quadrant of the right breast.

**Imaging features:**

- **Mammogram** on page 12 showed dense fibroglandular breast tissue but no focal abnormality (R1).
- **Targeted ultrasound** on page 13 showed a 16 mm well-defined hypoechoic solid lesion containing macrocalcifications. The appearances were considered indeterminate on ultrasonography (U3), but likely to represent a fibroadenoma. Ultrasound-guided core biopsy of the lesion revealed an invasive carcinoma with basal features and necrosis.
- **Breast MRI** confirmed a 16 mm lobulated tumour with a type 5 malignant tumour activity curve in the upper outer quadrant of the right breast.

**Surgical histology:** Right wide local excision confirmed a grade 3 invasive ductal carcinoma measuring 11mm, negative for ER and PR.

**Teaching points:**

- Breast cancer in young women can mimic benign disease and core biopsy is essential to secure a histological diagnosis.
• Dynamic contrast-enhanced MRI allows detailed evaluation of tumour enhancement kinetics. Malignant lesions tend to show a rapid uptake of contrast in the initial phase, followed by a rapid washout in the intermediate and late phase.

Case study 3

Clinical presentation: 38 year old presenting with a clinically indeterminate lump in the left breast at the 4 o'clock position.

Imaging features:

• Mammogram on page 16 showed a well-defined low density mass within the left breast (R2).

• Targeted ultrasound on page 17 showed a thick-walled but otherwise simple cyst situated deep in the left breast, considered benign on ultrasound imaging (U2). The cyst was aspirated to dryness under ultrasound-guidance, but the fluid was slightly blood-tinged and therefore sent for cytological analysis. Cytology revealed highly atypical cells suspicious for malignancy (C4). This was followed by an ultrasound-guided core biopsy of the posterior wall of the cyst that revealed an invasive carcinoma with papillary features.

• Breast MRI confirmed a 20mm unifocal cystic lesion in the lower outer quadrant of the left breast. The posterior aspect of the cyst wall was thickened and nodular with a type 4 suspicious tumour activity curve.

Surgical histology: Left wide local excision confirmed a 17 mm grade 3 invasive papillary carcinoma that was negative for ER, PR and HER2.

Teaching points:

• A simple cyst has a well-defined margin and a thin wall. It has no internal echoes and there is increased through transmission of the ultrasound beam reflecting its fluid content. Features of a complex cyst include the presence of internal echoes, thin septations or a thickened irregular wall.

• A cyst should be aspirated if the patient is symptomatic or if there is any diagnostic uncertainty. Fluid is sent for cytology only if blood-stained or if there are atypical sonographic features. Suspicious cytology from a cyst should not be dismissed and warrants further investigation.
Case study 4

Clinical presentation: 39 year old presenting with a clinically benign lump in the upper outer quadrant of the left breast.

Imaging features:

- **Mammogram** on page 20 showed extremely dense heterogeneous nodular breast tissue but no focal abnormality (R1).

- Targeted **ultrasound** on page 21 of the left upper outer quadrant was normal with no focal lesion (U1).

- As conventional breast imaging was normal with no correlate on mammography or ultrasonography to account for the patient's palpable lump, a clinical FNA was performed. Cytology contained malignant epithelial cells (C5).

- **Breast MRI** on page 22 was performed to localise the tumour and delineate tumour extent. This showed a 13mm unifocal circumscribed mass at the 2 o'clock position in the left breast. The tumour was morphologically indistinguishable from surrounding dense fibroglandular tissue, but it demonstrated malignant enhancement characteristics with a type 5 tumour activity curve.

Surgical histology: Left wide local excision revealed a 15 mm grade 2 invasive ductal carcinoma with neuroendocrine differentiation.

Teaching points:

- A palpable lump always requires full triple assessment. Even if conventional imaging is normal, a clinical core biopsy must be performed.

- If there is radiological and pathological discordance, where conventional imaging is normal then this warrants review of baseline imaging and MRI to assess disease extent.

- Breast MRI allows accurate sizing of the lesion and confirms the position of the tumour in the breast and its relationship to the nipple and chest wall, determining if the patient would be suitable for breast conservation.

Case study 5
Clinical presentation: 36 year old with a positive family history of breast cancer presents with a clinically indeterminate right breast lump at the 12 o’clock position.

Imaging features:

- **Mammogram** on page 23 showed a 25 mm spiculated mass in the right breast, consistent with malignancy (R5).

- Targeted ultrasound on page 24 showed a 17mm irregular hypoechoic mass with posterior acoustic shadowing, considered malignant on ultrasound imaging (U5). Ultrasound-guided core biopsy confirmed a grade 3 invasive ductal carcinoma.

- In view of the aggressive tumour profile in a young patient, neoadjuvant chemotherapy was advised following multidisciplinary team discussion. **Baseline breast MRI** on page 25 confirmed a unifocal 25mm mass at the 12 o’clock position in the right breast with a type 5 malignant tumour activity curve.

- **End of treatment MRI** on page 26 performed after 4 cycles of first line chemotherapy (Epirubicin/Cyclophosphamide) and 2 cycles of second line chemotherapy (Docetaxel/Herceptin) showed a complete radiological response.

Surgical histology: Right breast wide local excision was performed with hookwire localisation to the metallic marker clip that had been inserted after the first 2 cycles of neoadjuvant chemotherapy. The final histology demonstrated only a few residual tumour cells and fibrovascular tissue in keeping with treatment response.

Teaching points:

- Breast MRI is an accurate technique for monitoring response to neoadjuvant chemotherapy. The ability to closely monitor tumour behaviour is important in ensuring that operable disease does not progress to become inoperable whilst receiving neoadjuvant therapy.

- After the first 2 cycles of chemotherapy, if there is a good response to neoadjuvant treatment and the patient is considered a suitable candidate for breast conserving surgery, a metallic clip is placed in the shrinking tumour to act as a marker for wide local excision.

- Surgery remains an important part of the treatment pathway, as a complete response on MRI does not always equate to a complete pathological response.
Images for this section:

**Fig. 0:** Right MLO projection showed moderate density breast tissue, but no focal abnormality (R1).

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Fig. 0: Targeted ultrasound of the right breast showed a 16mm poorly defined irregular hypoechoic solid mass with posterior acoustic shadowing, consistent with malignancy (U5).

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**Fig. 0:** Contrast-enhanced MRI showed strong background fibroglandular enhancement in both breasts with a unifocal tumour in the right breast.

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**Fig. 0:** Contrast-enhanced MRI confirmed a 15mm unifocal irregular solid tumour with a type 5 malignant tumour activity curve in the right breast.

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Fig. 0: Right CC projection showed dense fibroglandular breast tissue but no focal abnormality (R1).

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**Fig. 0:** Targeted ultrasound showed a 16 mm well-defined hypoechoic solid lesion containing macrocalcifications, likely to represent a fibroadenoma (U3).

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Fig. 0: Contrast-enhanced MRI confirmed a 16 mm lobulated tumour in the upper outer quadrant of the right breast.

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Fig. 0: Dynamic contrast-enhanced MRI demonstrated a unifocal tumour in the right breast with a type 5 malignant tumour activity curve. Malignant lesions tend to show a rapid uptake of contrast in the initial phase, followed by washout in the intermediate and late phase.

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Fig. 0: Left MLO projection showed a well-defined low density mass within the left breast (R2).

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Fig. 0: Targeted ultrasound showed a thick-walled but otherwise simple cyst situated deep in the left breast, considered benign on ultrasound imaging (U2).

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Fig. 0: Contrast-enhanced breast MRI confirmed a 20mm unifocal cystic lesion in the lower outer quadrant of the left breast.

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**Fig. 0:** Contrast-enhanced breast MRI demonstrated the posterior aspect of the cyst wall was thickened and nodular with a type 4 suspicious tumour activity curve.

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**Fig. 0:** Left MLO projection showed extremely dense heterogeneous nodular breast tissue but no focal abnormality (R1).

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Fig. 0: Targeted ultrasound of the left upper outer quadrant was normal with no focal lesion (U1).

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**Fig. 0:** Contrast-enhanced breast MRI showed a 13mm unifocal circumscribed mass with a type 5 malignant tumour activity curve at the 2 o'clock position in the left breast.

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Fig. 0: Right MLO showed a 25 mm spiculated mass in the right breast, consistent with malignancy (R5).

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**Fig. 0:** Targeted ultrasound showed a 17mm irregular hypoechoic mass with posterior acoustic shadowing, considered malignant on ultrasound imaging (U5).

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**Fig. 0:** Baseline contrast-enhanced breast MRI confirmed a unifocal 25mm mass at the 12 o'clock position in the right breast with a type 5 malignant tumour activity curve.

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**Fig. 0:** End of treatment MRI showed a complete radiological response.

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Conclusion

Breast cancer in young women tends to be associated with genetic mutations including BRCA1 and BRCA2. The tumours are more likely to be poorly differentiated, hormone receptor negative and demonstrate lymphovascular invasion. Mammography is less sensitive in younger women due to the higher breast parenchymal density. Breast cancer in young women can mimic benign disease and triple assessment including core biopsy is essential to make the diagnosis. Breast MRI adds valuable information with accurate assessment of disease extent and evaluation of response to neoadjuvant chemotherapy.
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References


