Triple negative breast cancer diagnosis

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Learning objectives

With reference to various authors, the relevance of triple receptor negative breast cancer is 10-26%.

This cancer is difficult to diagnose, because sometimes it has no specific imaging signs usual in breast cancer.

• The main goal is to present the imaging peculiarities on triple negative breast cancer
• To review the main radiological signs of triple negative breast cancer on mammography, ultrasound and MRI.
• Triple negative breast cancer can mimic a benign morphology on various radiologic modalities.
Background

Breast cancer is a heterogenic disease. Human breast tumours are histologically complex and have some main gene expression profiles that are likely related to different molecular features of mammary epithelium.

The use of microarray profiling of invasive breast cancer has identified five distinct subtypes of morphological similar tumours: luminal A, luminal B, normal breast-like, human epidermal growth factor receptor 2 (HER2) overexpressing, and basal-like (1). The basal-like subtype is characterized by negativity for estrogen receptor (ER), progesterone receptor (PR) and HER2 (1).

It is important to clarify the relationship between triple receptor negative (TRN) breast cancer and the basal-like phenotype. TRN breast cancer is a term based on clinical assays for ER, PR and HER2, whereas the basal-like phenotype is a molecular phenotype initially defined using cDNA microarrays. Although most TRN breast tumours do cluster within the basal-like subgroup, these terms are not synonymous (2). It should be noted that only about 85% of triple-negative phenotypic breast cancers are deemed to be basal-like when tested by appropriate immunohistochemical methods (3).

The main characteristics of triple-negative cancers in the literature illustrate the similarities between basal-like and triple-negative tumors, including the fact that they more frequently affect younger patients (<50 years), are more prevalent in African-American women, often present as interval cancers and are significantly more aggressive than tumours pertaining to other molecular subgroups (4).

A relative survival for women with triple-negative breast cancer is poorer than for women with other types of breast cancer, with 77% of women surviving 5 years after diagnosis versus 93% for other breast cancers (3).

Triple negative phenotype was associated with the development of recurrence and distant metastases, and a poorer Nottingham Prognostic Index (5).

It is vital to detect breast cancer in its early stage. And it is a challenge in triple negative breast cancer because of its imaging features. The purpose of this study was to review the imaging characteristics of triple negative breast cancers on mammography, ultrasonography and magnetic resonance imaging.

In our observations and data analysis of more than 400 patients with triple negative breast cancer, triple negative cancers are relatively large tumours (>2cm) at presentation, often grade 3 and with a high rate of node positivity, that correspond to the data of our It revealed that 63.57% of patients had large tumours at presentation (T>2cm in), dominant
type of tumour was invasive ductal carcinoma (87.24%), the majority of tumours were poorly differentiated (76.57%) almost half of patients had positive axillary lymph nodes at presentation.

Triple negative cancer is usually diagnosed at late stage because it has no specific imaging features at early stage and has aggressive course because of poor differentiation.

If to compare the proportions of breast cancers discovered initially by imaging (mammography or ultrasonography) and by clinical detection (clinician or patient at age #50. Patients with triple negative breast tumors have a much lower proportion of breast cancers first detected by mammography or ultrasonography than patients with other breast cancers (19.6% versus 36.0%) (6).
Findings and procedure details

Mammographic features

Combined mammographic and pathologic features suggest a more rapid pattern of carcinogenesis, which leads directly to invasive cancer, with no major in situ component or pre-cancerous stage (7). Thus leads to mammographic appearance with no microcalcifications.

Calcifications

TRN cancers are not associated with microcalcifications (7). Triple negative tumours are less likely to have an associated calcification compared with ER+ and HER2+, the difference being statistically significant (1). In particular, HER2+ breast cancers are more likely to be associated with calcifications. A study which analyzed only TRN cancers (10) found that this type appeared as calcifications only in 10 out of 85 (11.8%) cases. Another study (9) proposes even lower numbers - 3 in 43 (7%). In our experience only in 10% cases the cancer was associated with microcalcifications.

The lack of mammographic microcalcifications is concordant with the low incidence of associated ductal carcinoma in situ in TRN carcinomas (7). It reflects the biological differences that exist among breast tumour phenotypes and indicates that triple negative breast cancer is a distinct clinical entity. According to these investigators, the combined mammographic and pathological features of this cancer suggest a more rapid pattern of carcinogenesis that leads directly to invasive cancer, with no major in situ component or precancerous stage (1).

Focal asymmetries and asymmetric densities

Mostly triple negative breast cancers were seen as focal asymmetry (1, 9).

Visibility

TRN cancers are not always visible on mammograms: in Dogan study (9) cancer was visible on 39 (90.7%) of 43 mammograms. Yang et al. (7) noticed that mammographic tumour visibility was similar among all immunophenotypes. The part of not visible tumour was biggest in the TRN cancer group (5/38, 13%), while in the HER2+ group it was 3 out of 67 (5%) and in the ER+ group 6 out of 93 (7%).
Mass

Yang et al. (7) found that TRN cancers most commonly present as a mass in mammography (28/38, 85%). In the study by Ko et al. (1), most of triple negative tumours presented as well as a mass compared with ER+ and HER2+ breast cancers (43/87, 49% compared with 42/93, 45% and 7/65, 11%). The same findings concluded Dogan and Yand studies (9, 7).

Ultrasonography

Combined mammography or ultrasound imaging findings of a non-calcified mass that is seen as a markedly hypoechoic mass with a circumscribed margin can be used to predict the presence of triple-negative breast cancer (1).

Although this tumour can mimic a lesion with a benign morphology, its mammographic or ultrasound imaging recognition can assist in both the pretreatment planning and prognosis as well as contribute to a better understanding of the biological behaviour of the disease entity (1).

Kojima and Tsunoda (10) identified a small number of patients (according to their mammograms) who were diagnosed with cancer without any abnormalities on mammography. If this happens in a normal screening process, such patients might slip through undiagnosed. Authors noted that ultrasound did indeed pick up all abnormalities. As a result, they concluded that ultrasound used in combination with mammography is advantageous in detecting triple negative cancer. Mammography and ultrasound imaging together have shown that the morphological features of triple negative tumour include a lobulated mass, with less attenuating posterior echoes, some vascularity, and low elasticity (10).

Despite their large size at presentation, triple receptor negative cancers may be occult in mammography or sonography and frequently have benign or indeterminate features (9).

In three studies (1, 9, 10), on ultrasonography more than 85% TRN breast cancer patients presented with masses.

Analyzing the attenuating posterior echoes in a study by Ko et al. (1) show that posterior shadowing was least common in triple negative breast cancers as compared with the other two types of lesions (1).
*Orientation* is evaluated according to skin (parallel or not parallel to skin). For triple negative cancer, the most common orientation is parallel (1). Parallel orientation is more characteristic of a benign process. TRN cancer appears as parallel, and this feature impedes its diagnostics.

The *vascularity* feature was analyzed by Kojima and Tsunoda (10). Hypervascularity was identified in 10 out of 80 (12.5%) TRN cancers, avascularity in 8 out of 80 (10%), spotty signals in 29 out of 80 (36.3%), and hypovascularity composed the biggest part (33/80, 41.2%).

In the study by Kojima and Tsunoda (10), among the patients who were able to have *elastography*, triple-negative tumours appeared as hard masses, with elasticity scores of 4 or 5. Such elasticity score of triple-negative tumour is as high as that of ordinary invasive ductal carcinoma (10).

**MR imaging findings**

MR findings of a unifocal lesion, mass lesion type, smooth mass margin, rim heterogeneous enhancement, persistent enhancement pattern, and a very high signal intensity on T2-weighted images are typical features of breast MR imaging associated with TRN breast cancer.

Although it can mimic a benign morphology, its early MR imaging recognition could assist in both the pretreatment planning and the prognosis, as well as add to our understanding of its biological behaviour (11).

Uematsu's et al (12) conclusion: several MR imaging features might be used for detecting triple negative breast cancer. Their study results have shown that several MR imaging findings, such as mass lesion type, smooth mass margin, rim enhancement, persistent enhancement pattern, and intratumoral necrosis, are suggestive of histopathologically triple negative breast cancer. Their study has shown that several MR imaging findings can be used for detecting this cancer (12,13). Authors noted that unifocal lesions are significantly associated with triple negative breast cancer in comparison with ER-positive / PR-positive / HER2-negative (HER2-). In our observations, triple negative cancers usually present as unifocal mass.

Several studies have shown that triple negative tumours most often present as mass enhancement and less commonly as non-mass-like enhancement (5,12,13).
In the study by Chen et al. (5), rim enhancement, a specific sign of malignancy on breast MR imaging, was identified in 41% of patients. Two other studies (10,12,13) mentioned not only rim enhancement, but also other types of internal enhancement, such as homogeneous and heterogeneous. In our observations we have noticed both homogenous and heterogeneous type of mass enhancement.

The smooth mass margin tends to be associated with TRN breast cancer. This is important because a smooth border of a mass is frequently used as indicative of a benign lesion. High-grade tumours, such as triple negative and familial breast cancer, are likely to manifest benign morphologic features (11).
**Fig. 1:** Recurrent triple negative cancer associated with microcalcifications

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**Fig. 2:** Magnifications image: triple negative cancer associated with microcalcifications.

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Fig. 3: Triple negative tumor in the upper lateral quadrant, appearing as an asymmetric density.

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**Fig. 4:** Triple negative tumor in the upper lateral quadrant, appearing as an asymmetric density.

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**Fig. 5:** Triple negative breast cancer appearing as a well circumscribed mass. Initially was interpreted as fibroadenoma.

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Fig. 6: Triple negative breast cancer appearing as a well circumscribed mass.

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Fig. 7: Triple negative breast cancer, appearing as a mass with no posterior enhancement, no speculated margins. Interpreted as BIRADS 4a on ultrasound examination.

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Fig. 8: Triple negative breast cancer; elasticity score 4-5.

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Fig. 9: Triple negative breast cancer appearing as irregular mass with little vascularity.

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**Fig. 10:** Triple negative breast cancer appearing as a large mass at presentation with rim enhancement.

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**Fig. 11:** Triple negative cancer appearing as unifocal mass with rim enhancement.

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Conclusion

Triple negative breast cancer is difficult to diagnose at early stage, because at that time it usually has no specific imaging signs for breast cancer.

1. In mammography, usually about one fifth of triple negative breast cancers present as focal asymmetry. Not all cases of triple negative tumours are visible on mammograms and often present as a mass. TRN cancers that appear as masses are most frequently round, oval or lobular in shape with indistinct margins. Triple negative cancers aren't associated with calcifications. Architectural distortion isn't their characteristic feature. Identification of TRN cancer is complicated on mammograms because it usually hasn't typical malignant features, such as microcalcifications, irregular shape and spiculated margins.

2. In ultrasonography, most of TRN breast cancers present as masses. Under half of them have accentuating posterior echoes. Only few triple negative tumours show attenuating posterior echoes. Hypervascularity isn't a characteristic feature of these tumors. TRN breast cancer appears as hard masses, with elasticity scores of 4 or 5 on elastography images. TRN cancers usually appear as a parallel-oriented mass, a feature more characteristic of a benign process. TRN breast cancers are mostly irregular in shape and have a circumscribed margin.

3. On MR imaging, triple negative cancers more often present as unifocal lesions as a mass enhancement. Usually it is lobulated, round or oval mass. Rim enhancement, a specific sign of malignancy on breast MR imaging, is identified in the majority of these tumours that makes MRI a valuable tool in these tumors assessment. A very high intratumoral signal intensity on T2-weighted MR images is associated with triple negative breast cancer. The initially rapid enhancement with a washout pattern (a sign of malignancy) does not usually match with the TRN cancer type. The TRN subtype is more frequently associated with a higher pathologic stage of the nodal status than the non-TRN subtype.
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References
