Imaging findings of triple-negative breast cancers

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Purpose

The triple negative (TN) phenotype of breast cancer is defined by negativity of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor amplification (HER2 amplification). These tumors most frequently have basal-like profiles (about 85%). They are characterized by aggressive potential with high histological grade, poor prognosis and BRCA 1-related breast cancer (1). They represent about 10 to 15 % of breast cancers and 10 % in our institution. An accurate and earlier detection might be helpful for planned treatment and to improve the survival of these patients with TN breast cancers. Our purpose is to investigate the specific imaging features of this subtype that are not well known. There were only a few studies about the relationship between tumor subtype and imaging findings and they contain a relatively small numbers of patients and analyze usually only one or two receptors not all three. Thus, the aim of our retrospective study was to identify the imaging characteristics of TN cancers, on mammography, sonography and MRI, in comparison with the mostly frequent tumors (ER/PR positive and HER2 negative).
Methods and Materials

From July 2009 to December 2010, a retrospective review was performed for 72 consecutive TN patients with mammograms and ultrasounds available. For some patients, MRI was also available. We compare this population with a control group containing 72 ER/PR positive and HER 2 negative (ER/PR+/HER2-) patients randomly selected from the same period.

Two senior breast radiologists reviewed and recorded the data of these patients for each lesion, with knowledge of the clinical and pathologic findings.

We investigated data on age, tumor manifestation (palpable mass vs. lesion identified with mammography or sonography), histological type and grade of the tumor and especially imaging features in mammography, sonography and MRI (if this exam was performed).

Histological findings were classified as invasive ductal carcinomas (IDC), ductal carcinoma in situ (DCIS), both (IDC+DCIS), invasive lobular carcinomas (ILC), other (as example, papillary, tubular, mucinous carcinomas…), and the grade was recorded as low, intermediate or high. We used the findings from breast conserving surgery or mastectomy specimens as the reference standard. The cutoff point for ER and PR positive expression was 10%. HER2 status was graded as 0.

Mammograms were available for all patients. Two standard imaging (craniocaudal and mediolateral oblique view) were performed with additional views if necessary. We analyzed retrospectively breast density (fatty, scattered fibroglandular, heterogeneously dense, or dense) and the existence or absence of lesion according to American College of Radiology (ACR) Breast Imaging Reporting and Data System (BIRADS) lexicon(2). The lesions were described as masses (size, shape: oval, round, lobulated or irregular; and margins: circumscribed, microlobulated, obscured, indistinct, spiculated), microcalcifications (size), masses with microcalcifications, asymmetric focal densities (size) and architectural distortions (size).

Ultrasounds were available for all patients. We analyzed retrospectively ultrasound images and classified as masses and non-mass lesions. In the study, non-mass lesions were defined as lesions that showed focal heterogeneity distinct from normal breast parenchyma and we just specified there size. Conversely, masses were defined as space-occupying lesions in two orthogonal projections. We used ACR-BIRADS lexicon and specified size, shape (oval, round, lobulated or irregular), margins (circumscribed, microlobulated, indistinct, angular, spiculated), lesion boundary (abrupt interface or hyperechoic halo), echogenicity (hypoechoic, hyperechoic, complex) and posterior acoustic features (no change, enhancement or shadowing). We also analyzed Doppler vascularity and quantitative elastography when the data were available.
Breast MRI was available in 16 patients out of 72 TN group (22%) and in 12 patients out of 72 ER/PR+/HER2- group (17%). The imaging protocol consisted of an turbo spin echo T2-weighted non fat-suppressed sequence followed by an axial spin echo T1-weighted pre-contrast and five serial dynamic post-contrast sets after rapid IV bolus infusion of 0.1 mmol/kg of gadopentetate dimeglumine at a rate of 2ml/s. Delayed contrast-enhanced images with fat suppression on an axial plane were also obtained. After the dynamic scan was completed, subtraction images were generated.

We retrospectively analyzed images on PACS system. The lesion morphology and enhancement kinetic features were defined according to ACR-BIRADS lexicon with final classification. We described lesions as mass and non-mass lesions. For masses, we specified shape (round, oval, lobulated or irregular), margins (smooth, irregular, speculated), internal enhancement (homogenous, heterogeneous, rim enhancement), kinetic enhancement (visual analyze or kinetic curves after ROI positioning) and T2-weighted aspect (hypo or hyper). For non-mass lesions, we described size, distribution and internal enhancement.

All statistical analyses were performed with the use of statistical software (SPSS, Cary USA). We used Khi-deux or Fisher's for qualitative data and the Mann Whitney or Student t-test for quantitative data. P-values less than 0.05 were considered statically significant.
Results

Clinicopathological data

All patients were women, between 28-95 years old (mean: 56) for the TN group, and between 37-84 years old (mean: 60) for the ER/PR+/HER2- group (p=0.094).

Women with TN breast cancers had larger clinical masses (median 40 mm) than patients with ER/PR+/HER2- tumors (median 30 mm) (p=0.11).

The majority of TN cancers had a high histological grade (53/72; 84.1%) compared to (10/72; 15.9%) ER/PR+/HER2- (p<0.001).

The histological type was not statistically different in the two groups: IDC (TN: 79.2%; ER/PR+/HER2-: 69.4%; p=0.18) and IDC+DCIS IDC (TN: 12.5%; ER/PR+/HER2-: 8.3%; p=0.41). Conversely, there was much more ILC in the ER/PR+/HER2- group (18.1%) than in the TN cohort (1.4%) (p=0.0007).

Mammographic findings

The breast density was 50% class 1-2, 50% class 3-4 for the TN group, and 65% class 1-2, 35% class 3-4 for the RE/PR+/HER2- cohort (p= 0.064).

TN cancers were visible on 84.7% of the mammograms. They were occult in the remaining patients (15.3%). For the RE/PR+/HER2- group they were visible and occult for respectively 93.1 and 6.9% (p=0.11).

TN cancers frequently presented with masses (37/72; 57.4%). The shape was more frequently round, oval or lobulated (65.9%) for TN lesions (vs. 27% for ER/PR+/HER2- cancers,p<0.001) and more frequently irregular for ER/PR+/HER2- tumors (73%) (vs. 34.1% in TN group, p<0.001). TN tumors had indistinct margins (56.1%) more frequently (p<0.001). On the contrary, margins of masses in ER/PR+/HER2- cancers were spiculated in 70.3% (vs. 14.3% in TN tumors, p<0.001). Fig. 1, 2.

In both groups, microcalcifications, masses with microcalcifications, asymmetric focal densities (AFD) and architectural distortions (AD) were relatively rare.

There were more BIRADS 5 classifications in the ER/PR+/HER2- tumors (37/72; 51.4 %) than in TN lesions (19/72; 26.4%) (p=0.002).TN cancers had more BIRADS 4 classifications (41/72; 56.9%).

Sonographic findings
Cancers were occult in sonography in globally the same proportion in the two groups (TN: 5.6%; ER/PR+/HER2-: 9.7%) (p=0.35)

63 out of 72 (92.6%) TN cancers presented with masses and 5 (7.4%) patients exhibited non-mass lesions. ER/PR+/HER2-lesions showed a quite similar pattern: 86.2% with masses and 13.8% with non-mass lesions (p=0.22).

Notably, for masses, TN cancers more frequently had an round or oval shape (65.1%) (vs.25% ER/PR+/HER2- lesions, p<0.001) and RE/PR+/HER2- tumors had a more irregular shape (75%) (vs. 34.9% TN, p<0.001). TN tumors most commonly had circumscribed or microlobulated margins (47.6%), contrary to ER/PR+/HER2- tumors who mostly had indistinct, angular, speculated margins (76.6%). We found a significant association between lesion margins and immunophenotype (p=0.006). For lesion boundaries, TN cancers had more frequently an abrupt interface (69.8%) than ER/PR+/HER2- cancers (48.2%) (p=0.016). The second group had more hyperechogenic haloes (51.8%). The echogenicity of TN cancers was hypoechoic in 100% as for RE/PR+/HER2-tumors. The TN masses had no posterior acoustic features or enhancement in 48 patients out of 72 (76.2%)(vs.46.5% ER/PR+/HER2- lesions, p<0.001) and posterior shadowing was present in ER/PR+/HER2- cancers with 30 out of 72 patients (53.5%)(vs.23.8% ER/PR+/HER2- lesions, p<0.001). **Fig. 3, 4, 5.**

Doppler color was available in 33/72 TN and 28/72 ER/PR+/HER2-. It was positive (one or more vessels) in 28 patients, negative in 5 for TN tumors, and respectively in 15 and 7 patients ER/PR+/HER2- (p=0.14).

For 17 patients TN and 14 patients ER/PR+/HER2-, we could use the quantitative elastography technique of Shear Wave elastography (SWE). The small number of patients and the variability of the data (KPA measures were inside the lesion for some tumors and in the periphery of the lesion for others) ruled out the investigation of this parameter. **Fig. 6.**

There were more BIRADS 5 classifications in ER/PR+/HER2- tumors (39/72; 54.2 %) than in TN lesions (22/72; 30.6%) (p=0.004). TN cancers had more BIRADS 4 classifications (42/72; 58.3%).

Dynamic contrast-enhanced MRI findings

MRI was available for 16 patients TN (22.2%) and 12 patients ER/PR+/HER2- patients (16.7%). All cancers were detected on MRI in the two subgroups and showed significant abnormal contrast enhancement. For the TN cohort, 12/16 cancers (75 %) appeared as masses and 4/16 (25%) as non-mass lesions. For the ER/PR +/HER2- group, it was respectively 7/12 (58.3%) and 5/12 (41.7%). There was no statistic difference between the two cohorts (p=0.43).
The following MRI comparisons are qualitative only, statistical tests were not performed due to the small number of patients in each group.

The TN cancers with mass-like enhancement had round, oval or lobulated shapes in 41.7% of cases and irregular shapes in 58.3%. The same pattern was observed in ER/PR+/HER2- group with respectively 42.9% and 57.1%. Fig. 7.

In the TN group, the margins were most frequently irregular (75%) and much less often smooth (16.7%) or spiculated (8.3%). For the ER/PR+/HER2- group, there were less irregular margins (57.1%), the same percentage of smooth margins (14.3%), and more speculated margins (28.6%).

The TN masses appeared more frequently with high intratumoral signal intensity on T2-weighted in 5/11 (45.5%) than in the ER/PR+/HER2- group (0/7; 0%). An hyposignal T2 was observed respectively in 6/11 (54.5%) and in 7/7 (100%). Fig 8.

Among the TN cancers with mass, the most common internal enhancement pattern was rim enhancement (8/12; 66.7%) which was very different than ER/PR+/HER2- group (1/7; 14.3%). Otherwise, homogenous enhancement was observed in 3/12 (25%) of the TN cohort, and (4/7; 57.1%) of the ER/PR+/HER2- group, and heterogeneous enhancement respectively in 1/12 (8.3%) and in 2/7; 28.6%). Fig 9.

The dynamic pattern of enhancement was globally the same in the two groups, with 8/12 (66.7%) of type 2 (plateau) curves in the TN group and 3/7 (42.9%) in the ER/PR+/HER2- group, and with respectively 4/12 (33.3%) and 4/7 (57.1%) of type 3 curves (wash out). Fig 10.

For TN non-mass lesions, MRI showed 1/4 focal zone, 1/4 regional enhancement and 2/4 ductal enhancements. For the ER/PR+/HER2- group, it was respectively 1/4 focal zone, 1/4 ductal enhancement and 1/4 segmental enhancement.

Of 4 TN and 5 ER/PR+/HER2- cancers with non-mass lesions, the most common internal enhancement was homogenous (2/4 and 3/5). MRI showed also heterogeneous enhancement in 1/4 TN and for ER/PR+/HER2- non mass lesions and micronodular enhancement in the same proportion in the two groups.
Fig. 1: 32-year-old woman with palpable mass in right breast. Mammogram shows a dense round-shaped mass, with mostly circumscribed and partially obscured margins.

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Fig. 2: 32-year-old woman with palpable mass in right breast. Sonograms shows a complex round-shaped mass, markedly hypoechoic, with mostly circumscribed margins and soft on elastography. Biopsy confirmed TN cancer.

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Fig. 6: 47-year-old woman with TN ductal invasive carcinoma. Ultrasound image shows a solid irregular-shaped mass, with microlobulated margins, abrupt interface and no posterior acoustic feature. The periphery of the lesion is hard on elastography.

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**Fig. 9:** 35-year-old woman with palpable abnormality in the left breast. Axial T1-weighted post-contrast shows enhancing mass. Ultrasound-guided core biopsy confirmed TN invasive ductal carcinoma.

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Fig. 7: 35-year-old woman with palpable abnormality in the left breast. Axial T1-weighted pre-contrast shows a oval mass.

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**Fig. 8:** 35-year-old woman with palpable abnormality in the left breast. Axial T2-weighted MR image shows hyper intense oval mass with smooth margins.

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**Fig. 10:** 35-year-old woman with palpable abnormality in the left breast. Dynamic curve, type 2 (plateau).

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Fig. 4: 70-year-old woman with TN cancer. Ultrasound image shows round mass with indistinct margins, markedly hypogenicity, hyperechoic halo, no posterior acoustic feature, and positive doppler vascularity. The periphery of the lesion is hard on elastography.

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Fig. 5: 70-year-old woman with TN cancer. Ultrasound image shows round mass with indistinct margins, markedly hypogenicity, hyperechoic halo, no posterior acoustic feature, and positive doppler vascularity. The periphery of the lesion is hard on elastography.

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Fig. 3: 70-year-old woman with TN cancer. Mammogram of left breast shows round mass with indistinct margins.

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Conclusion

TN breast cancers had larger clinical masses as in Yang et al.’s study (5). Their histopathological grade was high as in the literature (1, 3, 4).

We found striking differences between TN cancers and RE/PR+/HER2- breast cancers. In mammography, TN cancers were usually seen as masses with round, oval or lobulated shapes, as in the literature (4, 5), with frequently indistinct margins, more so than others studies (4, 5) Their characteristics mimicked benign masses and reflected aggressive, rapidly proliferating tumors with pushing margins without stroma-reaction (6,7). Finally, TN cancers appeared on mammography like benign or intermediate lesions. As a result, we had to be suspicious even if just one sign existed.

In sonography, TN cancers appeared commonly like a mass, with oval or round shapes, and circumscribed or microlobulated margins, and hypoechogenicity (1, 8). In Sook et al.’s cohort, they usually had irregular shapes (1). The TN masses commonly had abrupt interfaces and no posterior acoustic features or enhancement, like in other series (1, 4, 8). With these findings, some of these mass lesions might be misinterpreted as benign, similar to other subtypes of high grade tumors and familial breast cancers.

In MRI, we found that morphological criteria of TN masses were more suspicious compared to mammography and ultrasound with irregular margins and rim enhancement, even if statistical comparison was not possible due to the small number of patients. These findings were similar to those of Dogan et al. (8) and Chen et al. (9), but different to Uematsu et al. (3) who suggested a frequent association of smooth mass margins and rim enhancement. We also usually observed a T2-weighted hypersignal, like in Dogan et al.’s study (8) but this would need to be confirmed with a larger series.

A limitation of this study is the retrospective design but our primary aim was to identify the specific imaging characteristics of TN cancers which are aggressive with poor prognosis and so need to be diagnosed as early as possible, although accurate diagnosis is difficult. TN carcinomas more often have benign or intermediate characteristics in mammography and sonography. However, often there are small discrete signs indicating malignancy meaning that core biopsy must be performed. On MRI, their aspects are most typically malignant, usually with irregular margins and rim enhancement, suggesting that imaging techniques may be the most accurate for diagnosis of TN cancers.

Incorporation of clinical and histological data with molecular subtypes, and imaging specific features should potentially guide the therapeutic approach and facilitate prognostic assessment and patient outcome.
References


