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Radiological features of triple-negative breast cancers (73 cases)

M. Boisserie-Lacroix, G. Mac Grogan, M. Debled, S. Ferron, M. Asad-Syd, V. Brouste, S. Mathoulin-Pelissier, G. Hurtevent-Labrot

Abstract

Objectives: Triple-negative breast cancers generally occur in young women and they have the potential to be aggressive. It is important for this subtype of tumour to be detected early. We studied the appearance of 73 tumours on mammography, sonography and MRI in order to determine what specific features they showed on imaging.

Patients and methods: From July 2009 to December 2010, we retrospectively reviewed mammograms and sonograms of 73 triple-negative cancers. Colour Doppler had been used to depict vascularisation in 34 cases and elastography score calculated in 17 cases. Sixteen patients had undergone MRI. The radiological description of these different modalities draws on the BI-RADS lexicon and categorisation.

Results: On mammography, triple-negative cancers often presented as a round mass (59.3%) or an oval or lobulated mass (65%), with circumscribed (15%), microlobulated (12.5%), indistinct (55%) or occasionally spiculated margins (15%). On sonography, the vast majority of these cancers appeared as masses (92.8%) with occasional posterior acoustic attenuation (22.6%). MRI showed more suspicious images than the standard examinations, notably rim-enhancement (eight out of 12 masses).

Conclusion: Radiological images appear as lobulated masses more readily, while on sonography posterior enhancement is shown more often than attenuation, and MRI finds rim-enhancement.

KEYWORDS

Breast; Triple-negative cancer; Mammography; Sonography; MRI

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Current management of breast cancer has seen progress as molecular biology has developed. Breast cancer has become a heterogeneous illness with subtypes identified according to the presence of oestrogen or progesterone receptors, and whether or not the HER2/neu gene is expressed, without proliferation being considered. Tumours that neither express hormone receptors nor overexpress the HER2 gene are known as “triple-negative” (TN).

In fact there are a number of ways to define TN tumours:

- **anatomical pathology definition:** the threshold for a cancer to be considered non-hormone sensitive and TN is having less than 10% hormone receptors. HER2 status is determined using immunohistochemistry (IHC) and if the result is ambiguous (i.e. 2+) fluorescence in situ hybridisation (FISH) is used for final confirmation;
- **molecular definition:** the basal-like subtype accounts for 56–85% of TN cancers [1]. Analysing transcriptome expression profiles of invasive carcinomas has led to five major molecular subtypes being identified. These are luminal A, luminal B, ErbB2, basal-like and normal-like. The basal phenotype expresses high molecular weight cytokeratins (CK) (intracellular fibrous polypeptides) or basal CK (so-called because they are expressed in the basal or myoepithelial cells of normal lactiferous ducts). Basal-like carcinomas are characterised by the absence of expressed oestrogen and progesterone receptors and ErbB2. Nonetheless, some rare TN carcinomas do not express basal markers;
- **molecular and anatomical pathology definition.**

TN cancers represent 7–15% of all breast cancers [2,3]. In our center, the figure is 9%. At diagnosis, patients are of younger median age and the tumour is larger, which fits in with the concept of this tumour subtype as more aggressive. Furthermore they are often grade III tumours or very similar. TN cancers make up 70% of tumours found in women with the BRCA1 mutation [2,3]. Early detection of these cancers is vital due to their rapid progress, even though there is currently no targeted treatment, with neoadjuvant chemotherapy usually being indicated. TN cancers respond well to chemotherapy and those that respond less well reoccur sooner. TN tumours have a higher potential for metastases, particularly in the lungs and the brain [3].

If it is true that in a short time there has been a great deal written on TN tumours in the literature of molecular biology and clinical oncology, the same cannot be said for correlations between tumour subtypes and imaging. It is for this reason that we have undertaken this work: in order to define the radiological features of TN tumours.

**Methods**

**Patient selection**

We undertook a retrospective and descriptive review of the notes of 100 TN cancers diagnosed between July 2009 and December 2010, research which was drawn from a database at the Institute. For a case to be included we had to be able to read both the mammogram and sonogram (69 patients, 73 cancers) and have available to us any films taken outside of the centre or any examinations carried out in the department (Hologic Selenia digital full-field mammography system/SuperSonic Imagine ultrasound system) and stored on the image network (PACS Agfa). As for elastography, we only included the examinations done in our institution using the Shear-Wave technique. In addition to these standard examinations, we had MRIs available (reread on the image network) in 16 cases. Where anatomical pathology results were taken into consideration, these were the analyses of a tissue sample biopsy.

**Reading and interpretation**

The reading was shared between two senior radiologists from the department, and was done retrospectively, with knowledge of the anatomical pathology results. An interpretation form was drafted first, using the BI-RADS descriptive lexicon and ACR classification for each modality (mammography, sonography, MRI) [4]. When a patient presented two tumours, a form was completed for each tumour. Colour Doppler assessment of vascularisation had been carried out in 34 cases, and interpretation was fifty-fifty (vascularised — non-vascularised tumour). The elastography score in kPa had been measured in 17 cases, either of the intrallesional and/or perilesional area.

**Statistical interpretation**

We used the Clinical and Epidemiological Research Unit for statistical interpretation of the results.

**Results**

**Clinical aspects**

In 25 cases out of 73, the patient had discovered the tumour herself. One patient presented a BRCA 1 mutation. In 32 cases (43.8%), it was the right side that was affected and the left side in 41 cases (56.2%). Localisation was predominantly in the upper outer and inner quadrants (46.6% and 17.8% respectively). The tumours were easily large in size (10 to 150 mm, median 40 mm).

**Histologic type**

TN cancers were split into histologic types: the most common was invasive ductal carcinoma (IDC) at (79.5%), associated with a ductal carcinoma in situ (IDC + DCIS) in 12.3%, invasive lobular carcinoma (ILC) in 1.4%, and 6.8% presented another type (medullary, sarcomatoid, intracyctic papillary apocrine carcinoma and two invasive apocrine carcinomas). These were grade 3 tumours in 72.6% of cases.

**Mammography**

Density was categorised following the BI-RADS classification: type 1 in 13.7% of cases, type 2 in 35.6%, type 3 in 43.8% and type 4 in 6.8%. The mammography was normal in 15.9% of cases. It showed a mass in 59.3% of cases, microcalcifications in 13.6%, a mass with microcalcifications in 10%, and the cancer appeared as an architectural distortion or focal
Radiological features of triple-negative breast cancers (73 cases)

Figure 1. Forty-five years old. Palpable nodule. Mammogram: round mass with circumscribed margins.

The masses ranged in size from 7 to 70 mm (median 20 mm), and were round in 17.5% of cases, oval in 37.5%, lobulated in 10% and irregular in 35%. The margins were circumscribed in 15% of cases, indistinct in 55%, microlobulated in 12.5%, obscured in 2.5% and spiculated in 15% (Fig. 1).

The BI-RADS category based on mammography was found to be 2 in 15.1% of cases, 3 in 1.4% (1 case), 4 in 56.2% and 5 in 27.4%.

Sonography

The sonogram was normal in 5.5% of cases. Abnormalities appeared as masses in 92.8% of cases and non-masses (diffuse changes seen in the ultrasound-defined structure) in 7.2%. Of the 64 highly hypoechoic masses, 49.2% were oval, 15.9% were round and 34.9% were irregular. The margins were most often microlobulated (39.7%) (Fig. 2) but some were indistinct (28.6%), irregular (19%), circumscribed (7.9%) or spiculated (4.8%). An abrupt interface was most common (71% of cases) as opposed to an echogenic halo (29%). Posterior acoustic changes seen were attenuation (22.6%), enhancement (35.5%), or none (41.9%). The colour Doppler scans carried out in 34 cases was positive (at least one vessel formation shown in colour) in 41.4%. The elastography system used in 17 cases found scores ranging from 0 to 175 Kpa in the intralesional area and from 50 to 232 Kpa in the perilesional area, and in eight cases the ratio was calculated ranging from 1.9 to 11.8.

The ACR BI-RADS sonography category was found to be 1 and 2 in 6.4% of cases, 3 in 4.8%, 4 in 58.7% and 5 in 30.2%. In eight cases, the addition of elastography meant that the BI-RADS category was found to be 5 instead of 4 (Fig. 3).

Figure 2. Forty-three years old. Palpable nodule: a: mammogram: mass with obscured margins; b: sonogram: irregular mass with microlobulated margins and high vascularisation.

Figure 3. Forty-eight years old. Sonogram: lobulated mass with microlobulated margins. Shear-wave elastography: high score.
MRI

Of the 16 cases that underwent MRI, the abnormality was seen as a mass in 12 of these (75%) and a non-mass in four (25%). Of the masses, six showed low signal intensity and five showed iso-signal or high-signal intensity on a T2-weighted sequence (one case could not be analysed). Size ranged from 10 to 60 mm, and shape was round in one case, oval in two, lobulated in two, and irregular in seven (58.3%); the margins were smooth in two cases, irregular in nine and spiculated in one case. The time-intensity curve was type 2 in eight cases and type 3 in four cases. The enhancement pattern was homogenous in three cases, heterogeneous in one case, and rim-like in eight (66.7%).

Of the four non-mass contrast enhancements one was focal, one was regional and two were ductal; the internal enhancement pattern was homogenous in two cases, heterogeneous in one, and stippled in one case.

We did not observe any additional homolateral or contralateral contrast enhancement.

Discussion

Many TN tumours are detected by the patient herself, further to mastalgia, a palpable mass or signs of inflammation [2,3]. These patients, often under the age of 50, do not benefit from regular mammography screening. Even among patients who do have mammography screening, we know that a considerable number nonetheless present with interval cancer [5]. Haakinson [5] studied 1222 cases of interval cancers and reported that patients who had a palpable nodule less than 1 year after a normal mammogram were notably the youngest, with more aggressive TN phenotypes (odds ratio of 2.25, confidence interval 1.18–4.2). Clinical examination of patients therefore remains of prime importance.

There are very few literature reviews concerning the radiological features of TN tumours. They are retrospective with varying methodologies:
- those without a control group:
  - 85 patients with mammography, sonography, qualitative elastography (Kojima) [6],
  - 42 patients with mammography, sonography, MRI (Dogan) [7],
  - 29 patients with MRI (Chen) [8],
  - 83 patients with a study of the kinetic features on MRI (Li) [9];
- those with a control group:
  - 38 patients aged under 45 with a mammogram, compared to 67 HER2+ patients and 93 R+ patients (28 of which were HER+R+) (Yang) [10],
  - 33 patients with a mammogram compared to 23 ER−HER+ patients (Wang) [11],
  - 87 TN with mammogram and sonogram compared to 93 consecutive ER+PR−HER− patients and 65 ER+PR+HER+ (Sook) [1],
  - 59 patients with MRI compared to 117 ER/PR−HERpatients (Uematsu) [12].

Investigation of our patient series addressed all of the imaging modalities even if not all of the patients had benefitted from all of the examinations.

Mammography features

Table 1 compares our results to those in the literature. A mass is shown to be the most common presentation. In our study mass shape was round, oval or lobulated in 75% of cases, which concurs with the literature in which these shapes are reported in 60–75% of cases [6,7,10]. We found circumscribed margins (8.2%) less often than in the literature (24–43%) [1,6,10] and, on the contrary, indistinct margins more often (31.1%), but this difference could be due to variability between clinicians interpreting findings. The broadly round shape of the masses can be explained by the rapid growth of these tumours that do not develop stromal reaction [13]. Furthermore, in terms of morphology, an appearance of pushing margins is often reported in basal-like tumours and those linked to a BRCA mutation [10]. A recent study correlating features on mammography to prognostic factors in patients with N− tumours (no axillary infiltration) showed that highly dense masses and circumscribed or microlobulated margins were associated with a high histologic grade (note that TN cancers are often grade III) and a negative hormone receptor status [13].

All the studies agree that spiculated masses are less frequent in TN cancers: 7.5% of the series reviewed by Kojima [6], and 8.2% of our series. Microcalcifications are also less common in TN. Sook [1] found a significant difference between TN cancers and two control groups (ER+PR−HER− and ER−PR−HER+) in terms of asymmetric density (more common in TN) and microcalcifications (less common), but no significant difference in terms of architectural distortions and absence of abnormalities on mammography. For Yang [10] the low incidence of microcalcifications in TN cancers correlates with the infrequency of ductal carcinomas

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Features on mammography of triple-negative phenotype cancers.</th>
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<tbody>
<tr>
<td></td>
<td>Number of cases</td>
</tr>
<tr>
<td>Yang, 2008 [10]</td>
<td>38</td>
</tr>
<tr>
<td>Dogan, 2010 [7]</td>
<td>43</td>
</tr>
<tr>
<td>Kojima, 2010 [6]</td>
<td>85</td>
</tr>
<tr>
<td>Sook, 2010 [1]</td>
<td>87</td>
</tr>
<tr>
<td>Our study, 2012</td>
<td>73</td>
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</table>
in situ: 82% of 38 TN cancers were IDC without DCIS, and we also found similar results (78.5% IDC without DCIS). The rapid growth, with no precancerous stage, also explains the low incidence of microcalcifications [10]. Microcalcifications inside a mass or isolated segmental type calcifications were more often associated with a ductal carcinoma in situ and a HER2+ status [13]. The rate of normal mammograms varied between the series (from 0 to 18%). A negative mammogram can be explained by dense breast tissue reducing the contrast thus producing a ”masking effect”, and by the rapid progression of these tumours which is not accompanied by architectural distortion.

**Mammographic density and TN cancer**

In Kojima’s series, class 2 breast density was seen in 41.2% and class 3 in 50.6% of cases [6], and we also found a predominance of classes 2 and 3. Breast density is considered to be an independent risk factor for breast cancer [14,15]. Ma [16] investigated whether breast density could be correlated with TN tumour subtype, using a computerised (and therefore quantitative) method to calculate density in 479 patients (and 376 controls). Women who had in excess of 60% mammographic density had a 2.46 times greater relative cancer risk than women who had less than 10% mammographic density. This association also held for R+, R−, HER+ and HER− tumours. Density was similarly positively correlated to the luminal A subtype (which has a better prognosis) and the TN subtype. Therefore the mammographic density-cancer risk association was not found to be stronger for any particular histologic subtype.

The biological basis underlying breast density is not established. Density is associated with factors of poor prognosis: large tumour, high grade, lymph node invasion [17], and relationship with hormone receptor status discussed above.

**Sonography features**

**Conventional sonogram**

The features are summarised in Table 2 and Table 3. In line with the results in the literature, we found the predominant presentation to be a mass, reported also in ER+PR−HER− cancers (84%) but less often with ER+PR−HER+ tumours (68%) [1]. In this latter HER+ group non-masses (slight changes to the ultrasound-defined structure) are the most common, as they are in ductal carcinomas in situ, and Sook puts forward the hypothesis that an intraductal presentation may be more common in HER+ tumours [1]. As was seen with mammography, we found a round/oval/lobulated shape to be predominant, seen in 65.1% of our series and in 70% of Wang’s as against 38% in HER+ cases [11]. We saw circumscribed margins less frequently than reported in the literature and microlobulated margins more often. Wang did not report circumscribed margins in the control group of HER+ cancers, of which 56% had spicular margins; Wang concluded that the significant association between HER+ and spicular margins meant that HER2+ status could be predicted when faced with receptor negative status [11]. In contrast to the other studies, Sook [1] found masses most commonly to be irregular, both in TN cancers (83%) and in the two control groups ER+PR−HER− and ER+PR−HER+. This marked difference could be due to variation in how observers use the BI-RADS classification, with Sook using the term ”irregular shape” for masses that we would instead have described as ”oval with microlobulated margins”.

The tumour-parenchyma interface was abrupt more often in TN tumours (84% of Shin’s series and 71% of ours) and HER+ tumours (91%) than in R+ HER− cancers (64%) [13]. Low incidence of a peripheral echogenic halo can be explained by rapid tumour growth.

Highly marked hypoechogenicity was more common in TN cancers in Sook’s series (48%) [1]. Shin established a correlation between hypoechogenic masses and high grade, but did not specify the degree of hypoechogenicity [13]. The structure defined on sonography may be heterogeneous with areas of necrosis, as was seen in five tumours out of 25 that were over 3 cm in Kojima’s study [6]. With regard to morphology, the basal-like cancer subtype is often associated with areas of necrosis that are usually centrally located, with an inflammatory peripheral lymphocytic infiltrate.

In terms of posterior acoustic changes, enhancement is often seen in TN cancers (35.5% of our series and 49% of Sook’s [1]) and in R−HER+ cancers (50%) while it is only reported in 29% of R+ HER− in Sook’s study [1]. This is consistent with Shin’s study: posterior acoustic enhancement is associated with high-grade tumours and receptor negative status [13].

In various studies the finding of calcifications on sonography is not mentioned. For Shin, finding calcifications on mammography and sonography has a significant association with HER2+ status [13].

In our series, one cancer of 10 mm had initially been categorised as ACR 3, but monitoring showed an increase in size. For Dogan, six out of 38 masses (15.8%) had features of a solid mass with a benign appearance [7].

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Normal sonogram (%)</th>
<th>Mass (%)</th>
<th>Mass and calcifications (%)</th>
<th>Non-mass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2008 [11]</td>
<td>19</td>
<td>21</td>
<td>79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dogan, 2010 [7]</td>
<td>44</td>
<td>6.8</td>
<td>86.4</td>
<td>4.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Kojima, 2010 [6]</td>
<td>80</td>
<td>0</td>
<td>92.5</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Sook, 2010 [1]</td>
<td>87</td>
<td>0</td>
<td>86</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Our study, 2011</td>
<td>73</td>
<td>5.5</td>
<td>92.8</td>
<td>0</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Colour Doppler

Kojima [6] is the only author who carried out Colour Doppler imaging, examining 80 cases. Tumours with no signal represented 10% of cases, while the majority of TN cancers presented a few colour spots (36.3%) or vessel formations (41.2%), but rarely showed marked vascularisation (12.5%). We found negative results on Colour Doppler in 14.7% of cases. For Shin, marked vascularity shown on colour Doppler is associated with a high grade and negative hormone receptors [13].

Elastography

Kojima [6] carried out qualitative (static, non-quantitative) elastography in 40 patients, obtaining a score of 4 or 5 in 87.5% of cases. We quantitatively measured the intra- and perilesional elastographic score or just the perilesional score when the tumour was too hard and the display overloaded. It is difficult to draw any conclusions given the limited number of cases.

Features on sonography and response to chemotherapy

TN cancers respond well to chemotherapy, but those that respond less well reoccur sooner. Few studies have attempted to predict response to chemotherapy based on radiological features. In the Yang cohort [9], 52 patients underwent neoadjuvant chemotherapy. No significant difference was noted in the morphological features of tumours that responded fully or otherwise to chemotherapy. Currently, radiological features cannot be used as predictive factors of response to neoadjuvant therapy.

MRI features

Using this modality, masses are once again found to be the predominant presentation, even more so than with conventional imaging: between 77.3% and 97% in the literature [7,8,12], and in 75% of our 16 cases. A high T2 signal was seen in nearly half of the masses in our series, and the same was found in the literature [7,8,12]. Dogan [7] attributes this high signal intensity to areas of necrosis, but histologic correlation was not investigated. In Uematsu’s study, the seven cancers out of 117 in the control group that also showed high T2 signal intensity were mucinous tumours without necrosis [12]. The presence of internal necrosis is considered to be a factor predicting poor prognosis, correlated to a reduced disease-free interval, to early spread of metastases, and to increased mortality (irrespective of whether there is lymph node involvement) [18,19].

Morphological criteria on MRI led to more suspicious findings than conventional radiology since in our study 58.3% of masses were irregular. We found irregular margins in 75% of cases and spiculated margins rarely, while Dogan found spiculated margins in 41.2% of cases [7]. Rim-enhancement is commonly reported, in 76.5% of cases for Dogan [7] and 80% for Uematsu [12] who did not find any incidence of this in the control group (although the comparison was made with R+HER− tumours, which generally have a good prognosis). We know that the positive predictive value of malignity is high with this type of enhancement. Moreover, it is associated with factors of poor prognosis [20]. Several studies have tried to establish relationships between rim-enhancement and histopathologic factors of prognosis. Chen [21] compared the MRI features of 51 consecutive R−cancers and 39 consecutive R−cancers, and found that this type of enhancement was more common in R− tumours without being statistically significant. However, for Teifke rim-enhancement is the criterion that most accurately predicts hormone receptor status, high grade and lymph node infiltration [22]. Teifke showed that tumours with rim-enhancement had a higher rate of microvessels peripheral to the tumour as opposed to in the centre, when compared to benign tumours; this means that it is not microvessel density that is higher overall in malignant tumours, but the ratio between peripheral and central vessels, and this gradient rises significantly in grade 3, R− and N+ tumours [22]. In Dogan’s study, of the 26 masses with rim-enhancement, eight also had internal septa enhancement [6]. Dogan did not use the BI-RADS categorisation but smooth contours and rim-enhancement would be considered a class 4 mass following the ACR; an irregular shape and rim-enhancement, or enhanced septa would be considered an ACR class 5 [23]. Finally, where kinetics are concerned, a type 3 time-intensity curve, which would lead to suspicion of malignity, (early intensity with washout) occurred in 91% of Dogan’s cases [6] and 100% of Chen’s [21]. We did not observe any type 1 curves either.

Non-mass-like enhancement patterns were heterogeneous in seven out of 10 cases for Dogan [7]. Uematsu did not find any heterogeneous enhancement [12].

Li [9] wanted to describe the characteristics of 16 TN tumours and 21 R+HER− tumours on dynamic MRI, putting forward the theory that some kinetic parameters reflect the vascular microenvironment and could determine indications for targeted therapies. In TN cancers, increased cellularity and neovascularisation was reported as well as higher
intracellular levels of VEGF (vascular endothelial growth factor) in TN tumours than in ER+PR+ tumours (× 3). This explains the presence of morphologically and functionally abnormal vessels, with multiple arteriovenous shunts. The Vc (meaning the fraction of the tumour occupied by extravascular and extracellular space) was significantly lower in TN cancers (this translates into more compact tumours whose microenvironment is highly cellular); this lower Vc was reported both in high and low grade TN cancers. Kcp (outflow rate constant) was higher in TN tumours, which means that the contrast product returned into the circulation quickly, pointing to increased capillary permeability. Ktrans did not increase. Vc was the best parameter for distinguishing TN cancers (91% sensitivity, 76% specificity). Li believes that anti-angiogenic treatments could be useful [9].

Looking at disease spread, Chen [8] noted suspicious lymph nodes in the axillary region in 48% of cases, TN cancers being N+ more often than the other subtypes.

The ability of MRI to detect further lesions compared to the standard examinations means it may be useful as a pretreatment investigation [3] but there is no study that highlights the potential of MRI to investigate multifocality and multicentricity in this type of cancer. Indeed, Billar [2] reported that multifocality was less frequent in this type of cancer (14%) than in R+ cancers (20%) although not considerably so. The literature is also lacking any studies looking into MRI in the post-treatment monitoring of these patients.

Limitations of the studies

Most of the studies are in agreement in acknowledging that small patient samples are a limitation. The absence of a control group is also one, and this is equally true of our study. TN tumours are often quite large (3 cm on average in Yang’s series) [9], and we do not know if the radiological appearance is the same for newly growing tumours: no correlation with size has been done. Finally, knowledge is limited on the incidence of associated ductal carcinomas in situ (DCIS).

Conclusion

TN cancers are a distinct entity. In imaging, some radiological characteristics that are predictive of this cancer subtype have been described in a small number of cases in the literature and radiologists should be aware of these: the appearance of a mass on mammography, sonography and MRI; clear or even marked hypoechoicinity, posterior enhancement; rim-enhancement on MRI, visible enlarged axillary lymph nodes. Some TN tumours that may be interpreted as being benign based on conventional radiological investigations may show suspicous features on MRI.

Our study is broadly in agreement with this data, but we would highlight the finding of a higher incidence of microlobulated margins, and the value of quantitative elastography. Besides characterising a mass and categorising it according to the ACR BI-RAD, from the first mammogram or sonogram it becomes important to be aware of radiological findings that are predictive of an aggressive tumour subtype like the TN phenotype in order to arrange the appropriate management for the patient as quickly as possible.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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