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Correlation between imaging and prognostic factors: Molecular classification of breast cancers

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Abstract The new molecular classification of breast cancers defines cancer sub-groups with a distinct prognosis and response to treatment. Studies on the literature deal with the imaging of each tumour sub-type. The radiologist should be familiar with them in order to adapt the care of an aggressive sub-type. In view of the current knowledge, the following have been significantly more often observed: mammographical spiculated mass with echogenic halo in luminal A sub-type; architectural distortion in luminal B sub-type; an irregular mass with indistinct margin comprising microcalcifications, with an abrupt interface in the sonography, or non-sonographic mass in the HER2 sub-type; a very hypoechoic, lobulated mass with indistinct or microlobulated margin, with an abrupt interface, sometimes pseudo-benign, in the triple-negative sub-type.

KEYWORDS
Breast cancer; Mammography; Sonography; Molecular classification

According to the WHO, the histological type and grade of the tumour are indispensible diagnostic and prognostic morphological elements in the treatment of breast cancer. The prognostic and predictive elements of the response to treatment are added to this, that is, in addition to the histological grade, the hormone receptors (oestrogen (ER) and progesterone (PR) receptors) and the HER2 status. Since 2000, the breast cancers, in particular invasive ductal cancers, have been reclassified according to their genomic alterations that underlie highly different prognoses. This is the molecular or “intrinsic” classification distinguishing the luminal A, luminal B, HER2 positive, basal-like, triple-negative sub-types.

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Genomic tests, determining a prognostic signature, have been developed that currently do not find any clinical application in France. However, correlations between this molecular data and the morphology, grade and immuno-histochemical profile of invasive carcinomas have been established.

The authors describe the radio-histological aspects of invasive carcinomas according to their “traditional” histoprognostic factors and then describe the new molecular classification that the radiologist should now be familiar with, if only to adapt the care of an aggressive tumoral sub-type. Recently, papers on the correlations between tumour sub-type and conventional imaging have been published on a regular basis. The studies in the literature are retrospective, the methodology differs, they are sometimes based on a fairly limited number of cases and, above all, do not necessarily use the same histochemical criteria for the classification according to tumour sub-type.

Correlations between imaging and “traditional” prognostic and predictive factors

At the beginning of the 2000s, several authors demonstrated that factors such as tumour grade and hormone receptors (oestrogens, progesterone) may influence the appearance in the imaging [1,2].

The grade

Grade I and II tumours, with a fairly slow development, present a stroma reaction with retraction of the normal parenchyma, responsible for the typical appearance of malignancy in imaging. In Lamb’s series, in the mammography, spicules were observed in 72% of the grade I and II vs 24% of the grade III [2] and, in the sonography, a peri-lesional hyperechogenic halo and a posterior shadowing were observed in 71% of the grades I and II.

Rapidly evolving, grade III cancers do not develop a stroma reaction and display a round shape. In Lamb’s series, in the sonography, 16% of them presented a circumscribed contour and 36% a posterior enhancement (vs 9% of the grades I and II) [2]. Therefore, in 2000, Lamb concluded that the grade III cancers have a “paradoxically benign” appearance. Recently, Irshad [3] demonstrated that cancers presenting a posterior enhancement have a 24-time-higher odds-ratio of being grade III (95% CI, 9.91–58.14; P < 0.01) compared with tumours without enhancement. The contribution of the colour Doppler should be taken into account: distinct vascularization (not quantified in the studies) in the colour Doppler is also associated with grade III [4] (Fig. 1).

Grade III is often associated with other factors of a poor prognosis. Shin [4] showed that very dense masses in mammography, with a circumscribed or microlobulated contour, with posterior enhancement in the sonography, are significantly observed in the grade III cancers presenting a negativity of the hormone receptors.

Recently, Evans correlated the mean stiffness as measured with shear-wave elastography with the tumoral grade. Grade III was significantly associated with high mean stiffness (mean value Emed: 148 kPa). The difference in hardness was more marked between grades I and II (85 and 139 kPa, respectively) than between grades II and III [5]. In a series of 337 invasive cancers, Chang also found a correlation between the high tumour grade and the high mean value stiffness [6].

The hormone receptors

The presence of hormone receptors (R+ tumour) is a good prognosis and indicates a hormone-sensitive tumour. Their absence is a less favourable prognosis. R- tumours respond better to chemotherapy.

In the imaging, R+ cancers are often irregular (80%) and have spiculated margins (68%), significantly more frequently than triple-negative cancers [7] (Fig. 2). A peripheral echogenic halo is noted in 64% of the R+HER— cancers [8]. Recently, Irshad [3] demonstrated that cancers presenting a posterior shadowing have an odds-ratio at least 9 times higher of having a hormone receptivity (95% CI, 2.09–40.81; P = 0.011) compared with tumours without posterior shadowing and cancers presenting a posterior enhancement have an odds-ratio of 8 of being receptor-negative for oestrogens and/or progesterone (95% CI, 3.97–18.11; P = 0.001) compared with tumours without enhancement.

Recently, Chang carried out a retrospective study on the hardness of invasive cancers in elastography by correlating the status of the receptors. He described a significant association between Emed and the negativity of oestrogen receptors (Emed = 167 kPa for R— cancers and 138.7 kPa for R+ cancers, P < 0.015). The correlation was not significant for the progesterone receptors [6].

The HER2 status

The over-expression of HER2 is a factor of a poor prognosis, a predictive factor of a response to anti-HER2 therapies, and a predictive factor of resistance to tamoxifene (by crossing between routes of transduction of oestrogen receptors and HER2). This sub-type of cancer benefits from...
The new molecular classification

Luminal type A

As regards to the phenotype, in clinical practice, this type corresponds to the tubular carcinomas, and invasive ductal carcinomas (IDC) or grade I or II invasive lobular carcinomas (ILC), expressing oestrogen receptors (R+), with a low proliferation index (Ki67 < 15%, interpreted in immunohistochemistry technique).

In the mammography, in Taneja’s study, the spiculated mass is significantly more frequent in the luminal groups (42%) than in the other sub-types [9]. In sonography, all the criteria of malignancy are often observed: irregular shape, angular or spiculated margin, echogenic halo, posterior shadowing [8]. The tumour-parenchyma interface reveals a desmoplastic reaction and thereby fairly slow growth (Fig. 3).

In his retrospective study on the hardness of invasive cancers in elastography, Chang correlated the Emed with the different molecular sub-types. He demonstrated that tumours with an Emed < 50 kPa were luminal sub-types [6].

Luminal B type

As regards to the phenotype, in clinical practice, this type corresponds to the grade II or III invasive carcinoma, expressing oestrogen receptors (R+), with Her2 Score 0, 1+, 2+ not amplified (luminal B HER2−) or amplified (luminal B HER2+), with a high index of proliferation (Ki67 > 15%). Carcinomas arising with BRCA 2 mutations often belong to this molecular type.

In Taneja’s study, the spiculated mass was significantly more often observed in the luminal groups than the other sub-types. They less often belong to the luminal B type (33%) than the luminal A type. Architectural distortion is less often observed in luminal B (31%) than in the other sub-types [9]. However, the luminal B group only included 44 cases in this study.

Figure 2. 67 years old. Discovery of a small irregular mass during a screening mammography. Grade I IDC, ER = 90%. Sonography: centimetric hypoechoic mass with angular margins and high intra-lesional elastographic value of 240 kPa.

"targeted" therapies, treatments directed against the relatively specific molecular anomalies of cancer cells, in this case molecules targeting the family of HER2 receptors.

With the development of the new molecular classification, studies have been carried out on the correlations between imaging and HER2 status.

Figure 3. 54 years old. Screening examination. Grade I IDC, ER = 90%, PR = 70%, HER2−, Ki = 5%, luminal A: a: mammography, spot-compression: stellate infra-centimetric mass ACR 5; b: sonography: hypoechoic mass, with indistinct margin, and hyperechogenic halo; c: elastography: Emed intra-lesional value of 70 kPa, peri-lesional value higher at 180 kPa.
In the sonography, an irregular shape (88% of the cases) and posterior shadowing (85% of the cases) was significantly observed [8]. However, the examination was carried out with a 7.5 MHz sound and the authors acknowledge that the results would certainly have been different with more recent equipment (Fig. 4).

The HER2 (non-luminal) type

As regards to the phenotype, in clinical practice, this type corresponds to the grade II or III invasive carcinomas, not expressing oestrogen receptors (R−), with Her2 Score 3+ or 2+ in FISH amplified immuno-histochemistry, whatever the Ki67.

In mammography, the mass with indistinct margins is the most common mode of presentation: 42% in Taneja’s series [9]. The presence of calcifications (polymorphous, in the mass or in clusters of segmental distribution) is significantly associated with an HER2+ status. Their presence, correlated with the associated intra-ductal component, may predict an HER2+ status when the HER2 score equals 2+ on the micro-biopsy (in immuno-histochemistry) [4].

In sonography, a rather irregular mass is observed. The margins are described in various ways in the literature. However, the assessment of the margins depends on the apparatus and the reading by the technician: significantly indistinct margins in 94% of the masses for Au-Yong [8], but spiculated masses in 56% of Wang’s cases [10]. The tumour-parenchyma interface is more often abrupt in R-HER2+ tumours (91%) than in the R+HER2− cancers (64%) [8]. The posterior enhancement is more often observed in R−HER2+ cancers (50%) than in the R−HER2− cancers (29%) in Ko’s study [11]. Finally, non-masses are most often observed in the HER2+ group: 32% vs 16% of the ER+PR−HER2−, perhaps because the intra-ductal component is more frequent [4] (Fig. 5).

In Shin’s study, several factors have been grouped to obtain a statistical power. In this way, a mass with indistinct margins is significantly associated with a high-grade, a R− status and HER2+ [4].

As regards to the elastography, in Evans’ series, enriched HER2 tumours have a higher Emed (160.3 ± 56.2 kPa) than luminal tumours (136.9 ± 57.2), as related to their less favourable prognosis [5].

Figure 4. 43 years old, self-palpation of a large right mass. Luminal B IDC (HER2−). a: mammography, centred image: right supra-areolar focal hyperdensity; b: sonography: non-mass of 4 cm.

Figure 5. 47 years old, palpable mass. IDC HER2+ (non-luminal). a: mammography, profile (post-clip before neo-adjuvant chemotherapy): mass with indistinct margin, presence of several polymorphous microcalcifications; b: sonography: oval 20 mm mass with indistinct margin.
The basal-like type

In clinical practice, this type corresponds to a determined histological phenotype: grade III IDC, little differentiated, R−, HER2−, with lymphocyte infiltrate, zones of tumoral necrosis, central fibrotic zone, and "pushing" margins (continuous front of tumour growth, without stroma reaction). It is a heterogeneous group comprising 85% of the BRCA1, medullary and metaplastic cancers.

In the mammography, Tanega observed less spiculated masses (13%) and more masses with an indistinct margin (47%) than in the luminal and HER2+ sub-groups [9]. In the sonography, the halo is significantly less frequent (19%) [8].

The triple-negative type

As regards to the phenotype, in clinical practice, this triple-negative (TN) sub-type corresponds to grade II or more often III or little differentiated, RE−, HER2− invasive cancers.

This is the sub-group most described in the literature. In the mammography, the mass is the most common presentation, round, oval or lobulate in 60 to 75% of the cases, with a circumscribed margin in 24% to 43% of the cases, attesting to its fast growth [12−16] (Fig. 6). Ko [11] found a significant difference between TN and control groups (ER+PR−HER− and ER+PR−HER+) for microcalcifications (less frequent since the TN tumour does not go through a pre-cancerous phase) and focal asymmetries in density (more frequent in the TN). However, the frequency of the microcalcifications in this sub-type is in various ways assessed in the literature: 11/105 cases (12%) of TN and 16/105 cases (16.8%) of the control group R+HER2− in the series by Boisserie-Lacroix et al. [12].

The rate of normal mammographies also varies according to the series (from 0 to 18%) [12−16]. The negativity of the mammography may be due to the "masking effect" of the breast density that reduces the contrast, and by the rapid progression of these tumours that are not accompanied by architectural disorganisation.

In the sonography, the predominance of the round-oval-lobulate mass is found in 65.1% to 70% [12−16], with an indistinct or microlobulated margin. The tumour-parenchyma interface is most often abrupt in TN tumours (71 to 84%) and the HER+ tumours (91%) than in the R+HER− cancers (64%) [4,14−16]. Very marked hypoechogenicity is most common: 48% of the cases in Ko’s series [11]. The ecostructure may be heterogeneous with zones of necrosis, as well in 5 out of the 25 cases of tumours over 3 cm in Kojima’s study [14]. Posterior enhancement is observed in 35.5% to 49% of the TN cancers and 50% of the R−HER+ cancers [12,14−16] while it is only noted in 29% of the R+HER2− cancers in Ko’s study [11]. This corroborates Shin’s study: posterior enhancement is associated with the high-grade and negativity of the receptors [4]. For Dogan, 6 of the 38 masses (15.8%) were characteristic of a solid mass of benign appearance [15] (Fig. 7).

Tamaki recently reviewed the characteristics of 45 cancers in patients presenting a mammography classified as ACRI, finding that the majority of cancers, in sonography, are accompanied by an oval or round non-spiculated mass corresponding to a TN phenotype and/or grade III cancers [17].

As regards to the elastography, in Evans’ series, the TN tumours had the highest Emed (169.1 ± 48.5 kPa). The hardness of the tissue seemed to be significantly correlated with the tumoral aggressiveness [5]. Initially, the lowest elasticity
was expected in the TN cancers and the highest in the low-grade luminal cancers that develop a desmoplastic reaction. In fact, the hardness of tissue involves complex mechanisms and combines tumour cellularity, density in microvessels, necrosis, fibrosis, etc.

The apocrine type

The more recent individualization is still incomplete.

Clinical implications for therapy

Breast cancer has become a heterogeneous disease with clinically pertinent sub-groups with their own prognostic impact. In imaging, beyond the characterization of a mass and its classification according to the BI-RADS category by the ACR, it is important, as of the first mammo-sonography, to be familiar with the predictive characteristics of an aggressive tumoral sub-type in order to organise the care as soon as possible for the patient. In particular, the TN type is rapidly evolving, of greater tumoral size, in young women, and should not be mistaken by the radiologist for a benign tumour.

With invasive breast cancer, the indication for adjuvant chemotherapy is based on the analysis of the ‘‘traditional’’ clinical and histoprognostic factors, and is decided on during the multi-disciplinary meeting on the recommendations of consensus recommendations (St-Gallen, St-Paul-de-Vence, etc.) aided by the use of adjuvant online software. In parallel, over the last decade, the expression profiles have helped define tumours with a different prognosis, opening the way to therapeutic strategies adapted to the tumour profile, and even to a prediction of the response or lack of response to chemotherapy. For example, in patients with a good prognosis, without lymph node invasion or with R+ and grade II tumour (luminal A and B), the high genome grade (genes associated with the proliferation and regulation of the cell cycle, high KI67) and the low genome grade now allow for the acceptance or rejection of chemotherapy.

Three genome analysis tests have been marketed. The price is high and not reimbursed by the national health. In France, they are not considered to be useable. Therapeutic trials are in progress (ex. MINDACT based on the ’’70-gene signature’’, Mammaprint) to validate the feasibility of genome analysis in everyday practice.

Conclusion

In view of current knowledge, the most frequent significant aspects are:

• stellar mammography mass—irregular mass with echogenic halo, in the luminal A sub-type;
• architectural distortion in the luminal B sub-type;
• irregular mammographic mass with indistinct margin comprising microcalcifications, with abrupt interface in the sonography or non-echographic mass in the HER2 sub-type;
• lobular mass with an indistinct or microlobulated margin, very hypoechoic, with abrupt interface, sometimes pseudo-benign, with a high mean stiffness value in the triple-negative sub-type.

TAKE-HOME MESSAGES

General ideas

• Breast cancers are classified into tumour sub-types according to their molecular characteristics.
• Immuno-histochemical results are used in clinical practice.
• Studies are published on a regular basis on the imaging aspects as a function of this new molecular classification.

Main results: statistically significant associations

• Very dense mass with a circumscribed or microlobulated contour, with posterior enhancement, and grade III R—.
• Spiculated mass and luminal sub-type.
• Calcifications and HER2+ sub-type.
• Round-lobular mass with very hypoechoic microlobulated margin with abrupt interface and TN sub-type.

Case report

36 years old. Mass discovered by self-palpation, at the union of the left outer quadrants, of 2 cm. No palpable axillary adenomegaly. Family antecedents in the mother at the age of 55. A sonography image is provided (Fig. 8).

Questions

1. How do you describe this mass in your report?
2. Do you classify this mass: BI-RADS ACR 3? ACR 4? ACR 5?
3. Worried because of the 1st degree family antecedent, the young patient requested surgical excision, but in

Figure 8. Sonography: oval mass, with microlobulated margin, very marked hypoechogeticity, with posterior enhancement, not strictly parallel. ACR 4.
2 months due to professional problems. What is your response?
4. Does this mass initially suggest: an adenofibroma/a phyllole tumour/an HER2+ cancer/a triple-negative cancer?

**Answers**

1. It consists of an oval mass, with a microlobulated margin, very hypoechogenic, with posterior enhancement.
2. The microlobulated margin, the very marked hypoechogenicity and the great axis that is not strictly parallel does not indicate ACR 3 classification but ACR 4.
3. The appearance is suspect, and suggests a high-grade malignant tumour due to the pseudo-benign characteristics, requiring quick treatment.
4. The sonography suggests a malignant triple-negative tumour. The core biopsy 14 G concludes as to invasive grade III ductal carcinoma, ER PR = 0%, HER2—.

**Disclosure of interest**

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

**References**