Correlation between MR imaging – prognosis factors and molecular classification of breast cancers

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Abstract
The molecular classification of breast cancers defines subgroups of cancer with different prognoses and treatments. Each molecular type representing the intrinsic signature of the cancer corresponds to a histological profile incorporating hormone receptors, HER2 status and the proliferation index. This article describes the correlations between this molecular classification obtained in routine clinical practice using histological parameters and MRI. It shows that there is a specific MRI profile for triple-negative cancers: distinct demarcation, regular edges, hyperintensity on T2 weighted signals and, particularly, a crown enhancement. It is important for the radiologist to understand this molecular classification, firstly because of the relatively suggestive appearance of triple-negative basal-like cancers in the molecular classification, secondly, and particularly, as cancers in patients with the BRCA1 mutation are often triple-negative meaning that the criteria for reading the MRI needs to be tailored to this feature of the cancers, and finally because the efficacy of MRI in assessing response to neoadjuvant chemotherapy depends on the molecular class of cancer treated.

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MRI plays an essential role in the local staging assessment of breast cancer, enabling a better evaluation of tumor size, revealing multifocal or multicenter lesions or demonstrating a contralateral lesion, which is found on MRI in 3 to 4% of patients [1]. In addition to this impact on treatment, MRI is of prognostic use: it is helpful in predicting early effectiveness of neoadjuvant chemotherapy, which has been shown in a recently published multicenter trial [2] and more generally it independently predicts relapse-free

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survival in patients with breast cancer [3]. Identification of prognostic factors is an essential decision-making factor in the treatment of breast cancers. In addition to the main morphological prognostic factors such as tumor size and the presence of lymph nodes, the treatment of breast cancers is based on a number of classical histological factors, which determine different prognoses and management. These "classical" histological factors are histological grade, the Ki67 proliferation index, estrogen (ER) and progesterone (PR) hormone receptors and HER2 status.

In addition to these classical histological features the molecular abnormalities of breast cancers, which can be examined by genomic tests are also included. Whilst these genomic tests based on analysis of the expression of analysis of RNA and DNA have limited applications in routine clinical practice at present in France, specific correlations exist between the histological profile (incorporating hormone receptors, HER2 status and the proliferation index) and the different molecular types of breast carcinomas representing their intrinsic signature and classified as luminal A, luminal B, HER2-like, basal-like and more recently, apocrine type [4—6].

The aim of this article is to describe the correlations between MRI and histology of infiltrating carcinomas according to the different conventional histological prognostic factors and then to describe the correlations between MRI and the different molecular types of infiltrating carcinoma. Finally, in a third section we will emphasize the practical impact of the radiologist’s involvement in this molecular classification through two specific situations: diagnosis in a patient with a mutation and monitoring neoadjuvant chemotherapy.

Correlations between MRI and classical histological prognostic factors

The factors studied are grade Ki67 proliferation index, hormone receptors and HER2 status.

Tumor grade

This is based on three histological, morphological features: tumor architecture with cell differentiation, the shape and size of the nucleus and the number of cells in division or exhibiting mitotic activity.

Classically, grade 1 tumors develop slowly with a large stromal reaction whereas grade 3 tumors are hypercellular with little stromal reaction and grade 2 tumors have an intermediary appearance, which is more similar to that of grade 1 tumors. All publications describe this appearance on MRI with spiculated outlines (Fig. 1) in grade 1 cancers [7]. This is not reported absolutely consistently in all series [8] for several reasons: tumor polymorphism, the fact that the small number of patients included in the different series do not always allow a statistically significant difference to be identified, and the conditions under which MRI is performed, as irregular or spiculated outlines can be more easily seen on high resolution matrix investigations (Fig. 2) on thin sections. Finally, the conditions under which the MRI is read and interpreted have a bearing as thicker sections and blurring due to subtraction may mask thin spicules seen on non-subtracted thin sections. The crown enhancement is also a classical sign of a rapidly growing tumor associated with a high histological grade (Fig. 3). This enhancement may be due to extensive angiogenesis in the periphery of

Figure 1. A 61-year-old patient with grade 1 infiltrating, ductal carcinoma of the left breast, Ki67 = 10%: a: axial section, T2 weighted image, architectural distortion in a small spiculated left infero-medial mass; b: axial section, subtraction at 3 minutes, homogeneous irregular mass enhancement with a partly spiculated irregular outlines.

Figure 2. A 55-year-old patient with grade 3 infiltrating ductal carcinoma of the right breast, Ki67 = 50%: a: axial section, T2 weighted image, small difficult to see supero-external mass; b: axial section, subtraction at 3 minutes, small homogeneous round mass enhancement; c: enhancement at 3 minutes in thin sections providing a better view of the irregular outlines.
Correlation between MR imaging: Prognostic factors and molecular classification

the tumor whereas the center is necrotic or fibrosed. This
crown enhancement classically associated with higher grade
tumors [9,10] is of particular value in pointing towards a
high-grade tumor when the tumor outlines are regular. This
is illustrated in a Japanese article [11] describing correla-
tions between MRI and histology. It is also not specific, as the
same finding may be seen in benign lesions such as inflamma-
tory cysts, cytosteatonecrosis and abscesses and it is also not
specific for high grade cancer as it may be seen in intra-cystic
 papillary cancers.

Analysis of the diffusion coefficient (ADC) on diffusion
imaging performs well to reflect tumor cellularity although
the results, which have been published are rather contra-
dictory. Whilst one study published over 10 years ago [12]
concluded that the ADC value correlated closely with tumor
 cellularity, other reports [13] have shown that ADC corre-
related with histological type and not with tumor cellularity
and found no correlation between tumor grade and the ADC
value.

The Ki67 antigen

This is a proliferation marker as it is present on cell nuclei
during the proliferation phase and absent from the nuclei of
quiescent cells. It is detected by the Ki67 antibody and the
Ki67 labeling index is defined as the percentage of nuclei
labeled by the Ki67 antibody. The correlations between
MRI appearances and this cell proliferation marker are "at
least" the same as those which exist with grade: "at least" as
the index is undoubtedly a better marker of tumor prolif-
eration and therefore as speed of growth than grade.
In one study which included 107 patients and examined
correlations between MRI appearances and prognostic fac-
tors [8], whereas no correlation was found between MRI
appearances and grade there was a trend towards spicu-
lated tumor outlines in patients with a Ki67 of under 15%
and with non-spiculated outlines in patients with a Ki67 of
over 15%. Similarly, an enhanced peripheral crown was seen
more often in patients with a high Ki67.

Hormone receptors

This is an important prognostic index but a factor, which
impacts even more on treatment as it dictates whether or
not hormone therapy is indicated. Chen et al. [14] compared
MRI appearances of ER+ an ER− cancers and found that the
commonest appearance in both groups was with a mass. No
ER+ carcinomas showed "non-mass" enhancement, which
was found in 18% of ER− tumors. The MRI appearances of
the ER− cancers reflected their aggressive nature: more
frequent kinetics showing a washout effect, larger size and
more frequent lymphadenopathy.

Similarly, a study [15] which examined correlations
between histoprognostic factors and annual MRI enhance-
ment found that the ratio of peripheral to central
microvasculature was significantly higher in grade 3 tumors
and in RH− tumors, explaining the annual enhancement.

HER2 status

This also has prognostic but particularly therapeutic impact
through targeted treatments. There are few publications on
the MRI appearances of HER2 positive patients compared
to other breast cancers [16,17] and even more so because
patients who over-express HER2 are often analyzed in two
different groups: one group of ER− PR− HER2+ phenotype
("HER2 enriched" or "HER2-like") and another subgroup of
luminal B patients who over-expressed the HER2 receptor.

In addition, the results which have been published are
very inconsistent as in the two studies which included most
patients, both published in 2012 [16,17] patients who over-
expressed HER2 had MRI appearances similar to those of
patients with "triple-negative" cancers in one study [16]
whereas the appearances of HER2 patients were similar to
those in luminal cancers in the other study [17].

Correlation between MRI and molecular
type of breast cancers

Luminal A

This molecular type represents the majority of invasive
luminal cancers. These are grade I invasive ductal can-
cers which express estrogen receptors and have a Ki67 of
<15% and also the infiltrating lobular cancers (Fig. 4). In
the majority of cases this type of cancer is seen as a mass
with irregular or spiculated outlines and irregular in shape
(Fig. 5), with heterogeneous enhancement, no peripheral
crown, no peri-tumor edema and no pronounced hyperin-
tensity on T2 weighted images.

Luminal B

In clinical practice this molecular type can be defined as
a grade 2 or 3 carcinoma, which expresses estrogen recep-
tors and has a Ki67 proliferation index of ≥15%. It should
be noted that carcinomas developing in the context of the

Figure 3. A 58-year-old patient with grade 3 infiltrating ductal carcinoma of the left breast, hormone receptors negative and no HER2
over-expression. Triple-negative basal-like cancer: a: axial section, T2 weighted image. Deep retroareolar tumor mass with non-spiculated
outlines on intermediary T2 weighted image with a few fluid microdroplets; b: axial section, subtraction at 3 minutes. Heterogeneous
contrast uptake with thin annular enhancement.
BRCA 2 mutation often belong to this molecular group and that patients who are HER2 positive and express estrogen receptors are also included in this group.

There is no published information distinguishing the MRI appearances of luminal A and luminal B tumors. The reports which describe rounder cancers with more regular outlines in patients with a high tumor grade and high proliferation index also include triple-negative phenotype patients in this group. No publications refer to the specific case of patients with hormone-dependent breast cancer and a high tumor grade and proliferation index.

**HER2 (non-luminal)**

Clinically, this profile represents the grade 2 or 3 infiltrating carcinomas which do not express estrogen receptors and which exhibit strong HER2 over expression (3+) on immunohistochemistry, or 2+ HER2 gene amplification by FISH (fluorescence in situ hybridization) or by CISH (chromogenic in situ hybridization), regardless of Ki67 index. The published reports [16,17] do not describe specific appearances for the HER2 tumors: in one study they resembled triple-negative tumors and in the other they resembled luminal tumors. There is however a trend towards greater "non-mass" enhancement with a prevalence of almost 30% of cases in one series [16] in which the cancers over-expressed HER2 (Fig. 6). This finding is not consistent, however, [17] and we have also found very predominant mass appearances in this population. In addition, more of these patients would appear to have peri-lesional edema than those with luminal cancers.

**Basal-like carcinoma**

In genomic terms, the basal-like carcinomas exhibit numerous genomic changes with loss of chromosome segments and a P53-gene mutation is seen in almost 100% of cases.

Morphologically, the basal-like carcinomas are ductal, usually grade 3, and poorly differentiated with a rolled back margin combined with areas of geographical necrosis which is frequently central and a peripheral lymphocyte infiltrate (Fig. 7). They exhibit pronounced nuclear atypia and have a high mitotic index.

Immunophenotypically they are often ER, PR and HER2 triple-negative, although 20% of triple-negative carcinomas do not express basal markers and conversely, non-triple-negative carcinomas can express basal markers. In addition, occasional forms of good prognosis carcinoma share the same basal-like phenotype (the cystic adenoid carcinomas and juvenile secretory carcinomas) (RF). In practice, it is
important to recognize the grade 3 triple-negative basal-like tumors, as these are chemo-sensitive (apart from anthracycline resistance) possibly due to their high proliferation index and/or high prevalence of \( P53 \) gene mutation.

Carcinomas which occur in a context of the BRCA1 mutation often belong to this molecular group.

The MRI appearance of triple-negative carcinomas is relatively specific, with a number of particular features [16–19]. Almost all have a mass appearance, and unlike other cancers the mass is rarely irregular in shape and its outlines are more often smooth than spiculated. An enhanced crown is found in 50% of cases as is hyperintensity on T2 weighted imaging (Fig. 8), possibly due to tumor necrosis (Fig. 9), which in itself is a poor prognostic factor [20].

On diffusion weighted images, Youk et al. [17] have shown that ADC is of greater value and is independently associated with the triple-negative type, although there is an overlap between the values in the different groups of cancer, which makes this finding of limited use in clinical practice.

The contradictory increase in ADC value compared to the expected hypercellularity in these tumors is due to necrosis of triple-negative tumors resulting in a fall in their tumor cellularity and increased diffusion.
Apocrine cancer

One group of ER—PR—carcinomas has been identified which is different from the basal-like tumors and has an apocrine signature, with activation of the androgen receptor signaling pathway which may open the way to future anti-androgen hormone treatments. HER2 amplifications are a common but not constant finding. The apocrine tumors are aggressive and often bulky with a high histological grade, emboli are found in 50% of cases and invaded axillary lymph nodes are also seen in 50% of cases. Relapse-free survival and overall survival is poorer than for the other types of cancer. This profile of cancer does not appear to have any specific radiological features apart from the fact that they are diagnosed at a locally advanced stage. To our knowledge there are no articles describing the MRI appearances of these tumors.

What is the clinical impact?

Whilst identification of the molecular subtypes of breast cancer impacts on management, the utility of predicting molecular subtype from MRI appearances is not as well accepted, as all of these tumors will in any event be biopsied. The tumor’s molecular subtype is then defined in clinical practice from the biopsy results as luminal A, luminal B, HER2-like, basal-like, or apocrine. A triple-negative cancer suspected before biopsy from MRI appearances (as with mammography or ultrasound appearances) could help to expedite and accelerate management. In practice, apart from the need for radiologists to understand the language used by other disciplines, understanding the correlations between MRI appearances and the molecular type of the cancer has clinical impact in two situations: diagnosis in patients with a BRCA 1 mutation and the MRI follow-up of patients receiving neoadjuvant chemotherapy, success of which depends on the molecular type of the cancer.

MRI screening in patients with a BRCA 1 mutation

The majority of carcinomas (85%), which occur in a context of the inherited BRCA 1 mutation share the immunophenotypic, morphological and molecular features of the basal-like tumors [21], with a very high prevalence of triple-negative cancers.

Conversely, carcinomas which occur in the context of the inherited BRCA 2 mutations usually belong to the luminal B type, explaining why the BRCA 2 cancers often have the same MRI appearances as sporadic cancers although the BRCA 1 cancers have specific MRI appearances and are typically rounded or oval in shape, with regular outlines, an enhanced peripheral crown and hyperintensity on T2 weighted images. This classical appearance, however, is not a constant finding and the BRCA 1 tumors can also appear identical to sporadic cancers [19,22]. The two most characteristic, although not invariable, appearances associated with the BRCA 1 mutation are peripheral crown enhancement and prepectoral tumor location [23].

MRI monitoring on neoadjuvant chemotherapy

The performance of MRI in assessment of response to neoadjuvant chemotherapy depends on the molecular class of cancer. This is an important factor, which radiologists need to understand as it may impact on surgical management after neoadjuvant chemotherapy.

Two large studies, one of which included 203 patients treated with neoadjuvant chemotherapy [24] and the other, which included 746 patients in a retrospective, multicenter study [25] reported entirely consistent MRI performance results, both for the diagnosis of complete response and for the correlation between residual tumor size on MRI and pathological anatomy: MRI provides a more reliable assessment of tumor response after neoadjuvant chemotherapy in HER2-like cancers or triple-negative cancers than in cancers which over-express hormone receptors.

Whilst diffusion weighted MRI appears to provide limited information compared to morphological MRI to assess late response [26], it may be useful in pretreatment prediction of tumor response to neoadjuvant chemotherapy as compared to the series described above, a small series has shown that a high ADC, reflecting high diffusion and suggesting large extracellular volume, is a significant predictive indicator for failure of the tumor to respond [27].

Figure 9. A 45-year-old patient with grade 3 infiltrating ductal carcinoma of the left breast, negative hormone receptors and no over-expression of the HER2 oncoprotein. Triple-negative basal-like cancer: a: axial section, T2 weighted image: bulky 75 mm heterogeneous tumor mass with extensive necrosis, hyper intense on a T2 weighted image. Bulky retropectoral metastatic lymphadenopathy; b: axial section, subtraction at 3 minutes. Annular contrast uptake associated with a large central necrotic component.
Correlation

Conclusion

In conclusion, the correlations between MRI appearances and the molecular classification of breast cancers need to be understood as some appearances are relatively suggestive of triple-negative breast cancer. These should be looked for particularly in patients with a BRCA 1 mutation and also because the performance of MRI is assessing the efficacy of neoadjuvant chemotherapy depends on the molecular profile of the cancer.

TAKE HOME MESSAGES

- Immunohistochemical results provide a reliable assessment of the molecular characteristics of the cancer: luminal A, luminal B, HER2-like and basal-like. The appearances of luminal A, luminal B, and to a lesser extent, HER2 tumors cannot be distinguished.
- There are suggestive signs of triple-negative basal-like cancer: round shape, distinct outlines, T2 weighted hyperintensity and peripheral crown enhancement.
- MRI performs better in the assessment of response to neoadjuvant chemotherapy in HER2, basal-like and HER2-like cancers than in luminal cancers.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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