Assessing Breast Cancer Phenotypes with MRI Biomarkers in Clinical Practice

Elizabeth Morris, M.D.

Chief, Breast Imaging Service, Larry Norton Chair & Professor of Radiology,
Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA

Introduction

Advances in our understanding of the human genome have transformed the way we understand and treat breast cancer. Today, oncologists and gynecologists are no longer saying "this is invasive ductal carcinoma," but they can classify each breast cancer as one of four molecular subtypes based on its genetic expression. In this context, breast MRI provides a highly valuable and non-invasive tool to differentiate between subtypes due to the differences in imaging phenotypes between subtypes. In addition, as the cancer subtype has a significant impact on the individual patient's response to the currently available treatment options, MRI biomarkers may be used to predict complete response to therapy including non-surgical options and improve patient outcomes.

Breast cancer subtypes

While every breast cancer is unique, breast cancer can be classified into one of four distinct subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) positive, and basal-like. Luminal cancers are the most prevalent breast cancer subtype, representing 70% (55% luminal A, and 15% luminal B) of all breast cancers. Non-luminal cancers are less common but still substantial, representing 30% (15% basal-like and 15% HER2) of all breast cancers (Fig. 1).

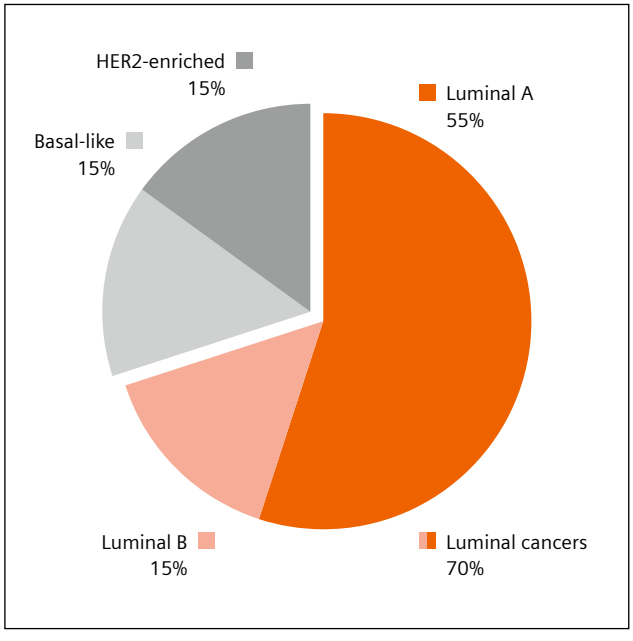
The breast cancer subtype that is present in an individual patient has a significant impact on the cancer's aggressiveness. HER2-positive cancers and triple negative cancers are more highly aggressive whereas luminal A cancers (which are the most frequently diagnosed breast cancer) have a relatively good prognosis. In addition to the subtype, it must also be noted that intracellular receptors that respond to estrogen (ER) and progesterone (PR) hormones as well as HER2 receptors have been shown to also impact cancer aggressiveness. All cells have HER2 receptors on them, but if they overexpress these receptors to a certain degree, then they are associated with a much more aggressive form of breast cancer with uncontrolled growth.

Luminal A

Luminal A cancers are low-grade cancers that are strongly ER positive and/or PR positive as well as HER2 negative. They show no amplification of HER2, the proto-oncogene for increased growth, or Ki-67, a biomarker for cellular proliferation.

Luminal A cancers have a five-year survival rate of over 80%, which is highest among the subtypes. Luminal A cancers respond favorably to hormone therapy with tamoxifen or aromatase inhibitors (AI). Nonetheless, they are associated with the risk of late mortality more than ten years after the original diagnosis. It is hypothesized that the cancer cells remain inactive for a long time, probably suppressed by the immune system, before late relapse takes place. Late relapse is not uncommon with this subtype and luminal A cancers are highly likely to metastasize to the bone.

On MRI, luminal A presents as a typical spiculated mass with significant desmoplastic response (Fig. 2).



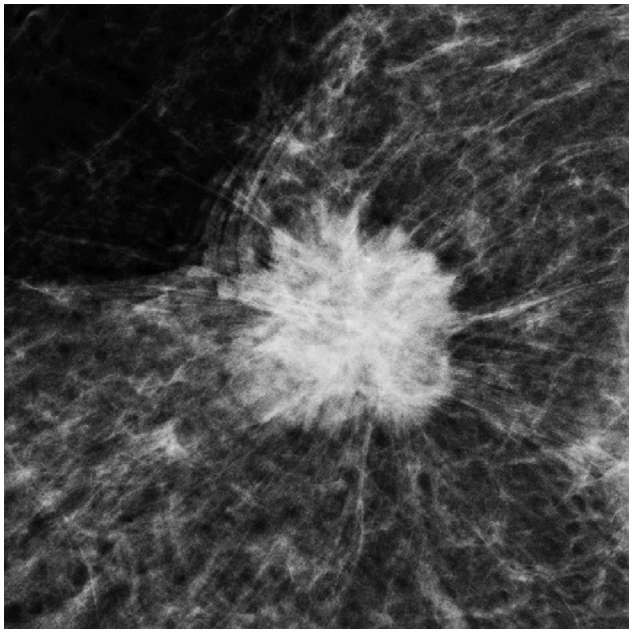
1 Breast cancer subtypes and their respective prevalence.

Luminal B

Luminal B cancers have a lower level of expression of ER and PR than luminal A cancers, and 20–30% of these cancers have a concomitant amplification of HER2. Compared with luminal A cancers, luminal B cancers are higher grade (always medium- to high-grade), showing a higher Ki-67 index and likely having lymph node involvement. Hence, luminal B cancers have a definite decrease in long-term survival, with a five-year survival of approximately 40%. Like luminal A cancers, luminal B cancers metastasize to the bone.

Mammoprint, Oncotype DX, and PAM-50 multigene assays identify breast cancers with an increased risk of recurrence based on gene expression arrays using formalin-fixed paraffin-embedded (FFPE) specimens. They help to identify which patient can forego chemotherapy. For luminal B cancers, a low Oncotype DX recurrence score permits the recommendation of hormonal therapy alone, whereas a high recurrence score indicates that chemotherapy is required as an adjunct treatment.

On imaging, luminal A and luminal B cancers look very similar. Tumor grading is the preferred mechanism for differentiating luminal A and luminal B cancers. Ki-67 can also provide great assistance but is not routinely recommended. Ki-67 as a prognostic marker is associated with larger tumor size, lymph node involvement, and shorter disease-free survival (DFS) and overall survival (OS). Ki-67 has shown to be positively associated with response to neoadjuvant chemotherapy (NAC).



2 Zoomed T1-weighted post-contrast images (subtracted from T1-weighted pre-contrast) showing the typical representation of a luminal A breast cancer: a hyperdense, spiculated mass with irregular margins and significant desmoplastic response.

HER2 positive

15% of all breast cancers are HER2 positive. These tumors usually have an intermediate to high nuclear grade. Prior to the introduction of traztuzumab (brand name Herceptin) and pertuzamab (brand name Perjeta), the untreated clinical five-year survival rate was 31%; with these treatments, treating physicians have achieved a 33% reduction in mortality and a 52% reduction in recurrence.

Patients with HER2 positive cancers are more likely to have metastases that go to the viscera and the brain.

Basal-like

The fourth subtype of breast cancer is basal-like. Basal-like cancers have cells that are similar to epithelial cells (i.e., basal cells) that line the surface of the basement membranes along the ducts.

While there are many different types of basal cell cancer, the clinical focus is on triple-negative invasive ductal cancers. The discussion of triple-negative cancers generally centers on the very aggressive nature of this cancer and that it is more common in African-American women. In this population, this cancer represents 27% of the overall cancer burden and 41% of the cancer mortality.

Adenoid cystic carcinoma is a rare type of invasive ductal cancer; however, while it is triple negative, it has very positive prognosis and outcome.

Basal-like breast cancer is usually high grade with an aggressive clinical course. Recurrence normally occurs in the first five years after diagnosis. Once a patient is beyond the five-year mark, the prognosis is normally positive; this is in stark contrast to luminal A type breast cancer. Basal-like breast cancer also has a high occurrence of metastases to brain, lung, and viscera. This subtype of cancer has the highest mortality rate.

The role of MRI and radiomics

Over the past few decades, breast MRI capabilities have improved dramatically. With radiomics and radiogenomics, MR images can now be analyzed so that the image is related to the genome, rendering a host of data that might positively affect patient outcome. Radiologists can identify volumes to be segmented on MR images. Computers can then extract hundreds of descriptive and quantitative features that, when combined with medical and genomic data, create a comprehensive database. Clinicians can compare pixels with adjacent pixels and analyze them in this context to render many different datasets.

As opposed to traditional human interpretation where radiologists interpret the shape, margin, internal enhancement patterns, and kinetic curve of the lesion, computers can automatically segment abnormal lesions and parenchyma in the MR image, produce data on kinetic features, and analyze morphological texture features rendering a

more quantitative phenotype analysis. Radiomics has provided deeper analytic features in datasets, e.g., inter- and intra-tumor heterogeneity, site entropy, kurtosis, and site cluster dissimilarity, by extracting information from images that is imperceptible visually. This information is combined with clinical data and genomic profiles to facilitate the establishment of a clinically applicable prognosis prediction model. For example, MR images of a patient pre- and post-NAC as shown in in Figure 3 could render feature data that provide the clinician with a greater ability to predict pathologic complete response (pCR) by showing whether viable tumor persists.

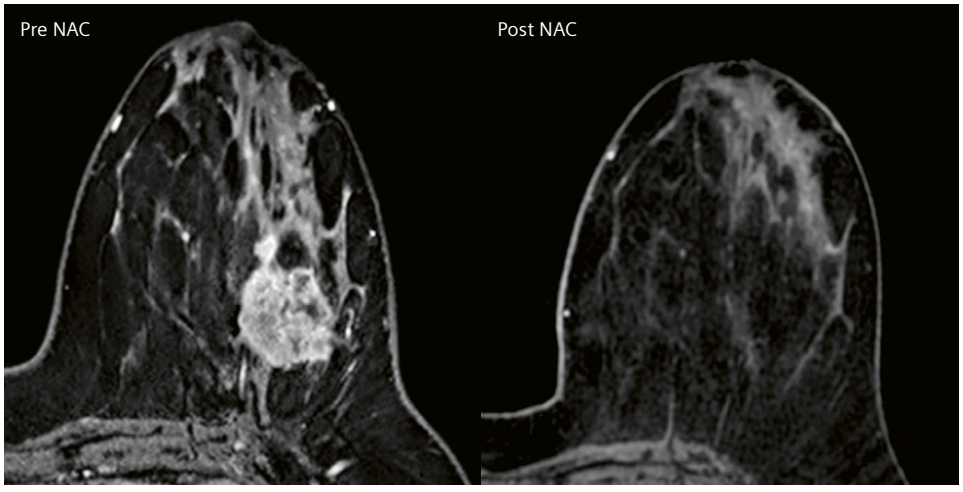
While radiomics encompasses numerous potential features, these features tend to be standardizable and quantifiable. Many research organizations have been investigating the utility of radiomics to determine breast cancer phenotype groups. At Memorial Sloan Kettering Cancer Center (MSK), we have found that clinicians are able to predict breast cancer phenotypes with radiomics nearly as accurately as Oncotype DX and PAM50. Therefore, it is possible that in the future radiomics could establish oncologic signatures in the same way that tissue sampling currently does but without the need for invasive procedures.

Neoadjuvant Chemotherapy

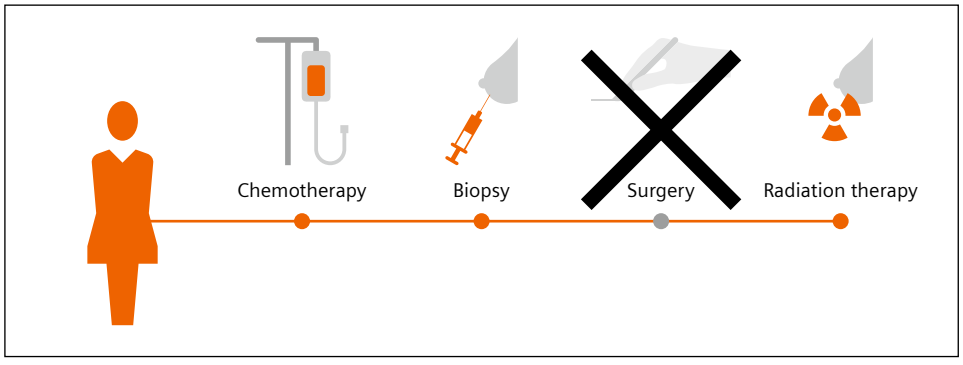
Neoadjuvant Chemotherapy (NAC) is increasingly used to treat breast cancer because it enables breast-conserving surgery in women who traditionally require a mastectomy. The goal of NAC is pCR, defined as the absence of any residual in-situ or invasive cancer. pCR has served as a surrogate of DFS and OS for a long time.

Currently, the most accurately predictive test for pCR is MRI. MRI is more accurate in determining residual disease than physical examination, mammography, and ultrasound [3, 6]. However, MRI is not universally utilized as it still renders many false positives and false negatives. The absence of enhancement on MRI is called a radiologic complete response (rCR) even when there is a residual mass, and the pattern of the residual tumor is defined as contiguous or scattered to allow for better surgical selection.

With radiomics, it is possible that clinicians will achieve better response prediction with MRI, and MRI could potentially be used to replace surgery in the identification of patients with a complete response. Preliminary studies at MSK have shown that radiomics may be able to differentiate responders from non-responders.



3 Subtracted, post-contrast T1-weighted images pre and post neoadjuvant chemotherapy. Patient showing complete imaging response which was confirmed as complete pathological response by biopsy. Highest response rates are seen in patients with TNBC and HER2+.



4 Proposed Care Pathway for patients with predicted pCR based on radiomic MRI profiling and biopsy-derived genetic profiling. In a planned trial patients shall proceed directly to radiation therapy without surgery.

New study conducted by Memorial Sloan Kettering Cancer Center

Currently, the NAC course of treatment involves MRI monitoring at critical points. We have been conducting a trial to perform a percutaneous MRI-guided biopsy in patients who have had an rCR as determined on MRI with radiomic analysis prior to surgery. We hypothesized that MRI-guided biopsy will accurately diagnose a pCR in women with complete response on MRI comparable to surgery, thus allowing us to avoid unnecessary surgery in these patients. For the pilot phase, so far ten patients have undergone the MRI-guided biopsy (with a marker to allow targeting of the biopsy) post NAC but prior to surgery. Results from the pilot phase indicate that MRI-guided biopsy can yield a high level of accuracy in diagnosing a pCR.

Therefore, we are currently proposing a full trial where the management of breast cancer in women with a pCR (as diagnosed by MRI-guided biopsy post-NAC) will proceed without surgery to the indicated duration of radiation therapy (Fig. 4). The salient open question is what quantity of residual disease precludes bypassing the surgical option for the less invasive method. Also, given that this would represent a new treatment protocol, the type of follow-up that would be required has yet to be determined.

Topics for further research

Another topic that is also worthy of further investigation is the association between parenchymal enhancement using contrast-enhanced MRI and the outcome of patients with breast cancer, as studied earlier by van der Velden et al. [4]. This study found that parenchymal enhancement is associated with long-term outcomes and higher parenchymal enhancement is associated with better outcomes. Women who have higher background enhancement who are treated experience better outcomes than women with lower background enhancement even though high background enhancement is associated with higher risk of developing breast cancer [4]. These results have been reproduced [5].

MRI features can also be investigated to predict cancer aggressiveness. For example, Lee et al. [1] found that spiculated margins were an indicator low grade ($p < 0.001$) and a low Ki-67 ($p = 0.007$); these are typical of luminal A breast cancers which have a high chance of pCR. Lee et al. also found that tumors with a high grade ($p < 0.001$) and that were ER negative were associated with poor patient outcome ($p = 0.001$).

Lastly, peritumoral edema, which indicates increased vascular permeability with local cytokines, is associated with early metastatic disease and can also be investigated for its clinical utility [2].

Conclusion

MR imaging is moving into an era of technology where the status quo is being disrupted. Artificial intelligence (AI) and machine learning will produce marked advancements in risk prediction and cancer detection.

As advances continue to be made in the tools available to clinicians, clinicians must task themselves to find uses for these advancements that will improve treatment options, patient outcomes, and quality of life. Clinicians must be intellectually agile to use these tools to create new possibilities for the treatment of patients as individuals, guiding clinical practice toward personalized medicine.

References

1 Lee SH, Cho N, Kim SJ, Cha JH, Cho KS, Ko ES, Moon WK. Correlation between high resolution dynamic MR features and prognostic factors in breast cancer. Korean J Radiol. 2008 Jan-Feb;9(1):10-8.

2 Rao A, Net J, Brandt K, Huang E, Freymann J, Burnside E, Kirby J, Morris E, Bonaccio E, Giger M, Jaffe C, Ganott M, Sutton E, Le-Petross H, Zuley M, Dogan B, and Whitman G. TU-CD-BRB-07: Identification of Associations Between Radiologist-Annotated Imaging Features and Genomic Alterations in Breast Invasive Carcinoma, a TCGA Phenotype Research Group Study. Med Phys. 2015;42:3603-4.

3 Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, Samulski TV, Dewhirst MW. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. AJR Am J Roentgenol. 2003 Nov;181(5):1275-82.

4 van der Velden BH, Dmitriev I, Loo CE, Pijnappel RM, Gilhuijs KG. Association between Parenchymal Enhancement of the Contralateral Breast in Dynamic Contrast-enhanced MR Imaging and Outcome of Patients with Unilateral Invasive Breast Cancer. Radiology. 2015 Sep;276(3):675-85.

5 van der Velden BH, Sutton EJ, Carbonaro LA, Pijnappel RM, Morris EA. Contralateral parenchymal enhancement on dynamic contrast-enhanced MRI reproduces as a biomarker of survival in ER-positive/HER2-negative breast cancer patients. Euro Radiology. 2018 Nov;28(11):4705-16.

6 Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, Halpern E, Moore R, Kuter I, Taghian A. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. AJR Am J Roentgenol. 2005 Mar;184(3):868-77.

Contact

Elizabeth Morris, M.D.
Chief, Breast Imaging Service, Larry Norton Chair & Professor of Radiology
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY, 10065
USA
Tel. +1 646 888 4510
morrise@mskcc.org