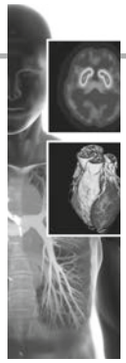

Imaging as a potential tool for subtyping breast cancer

"*...newer imaging techniques that are sensitive to tumor biology open the way to exciting developments in this field...*"

KEYWORDS: breast cancer ■ diffusion-weighted imaging ■ metabolic imaging ■ molecular subtypes ■ MRI ■ PET

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Breast cancer is increasingly being recognized as a collection of different diseases. For many years, medical oncologists have been used to considering hormone receptor (HR) status, HER2 status and markers of the cancer cell cycle, together with tumor size and metastatic spread to the axillary lymph nodes, to infer on prognosis and to assign adjuvant treatments. While these single factors are still looked at in decision making in current clinical practice, a more complex classification, which has been suggested by pivotal multigene expression analysis studies, allows a better recapitulation of breast cancer heterogeneity [1]. Perou *et al.* initially identified four distinct intrinsic breast cancer subtypes, which they called luminal A, luminal B, HER2-enriched and basal-like type, by analyzing gene expression profiles [1–3]. Subsequently, several other investigators have found that molecularly defined subtypes could be identified by the combined use of conventional immunohistochemical markers [4,5]. The luminal A subtype includes good prognosis hormone receptor positive tumors that are low proliferating. The luminal B subtype includes tumors that express HRs, but carry a more adverse prognosis because of higher tumor cell proliferation and/or HER2 positivity. The HER2-enriched (HER2-positive and negative HRs) and triple negative (HER2-negative and negative HRs) subtypes represent the most biologically aggressive subtypes of breast cancer. Science is further investigating the genetics of breast cancer, revealing more complex findings on the heterogeneity of this disease [6]. Meanwhile, the immunohistochemistry-based classification of luminal A, luminal B/HER2-negative, HER2-positive (either luminal or nonluminal) and triple negative subtypes has been proposed as pivotal in estimating prognosis and in assigning adjuvant medical treatments in women with operable breast cancer [7]. However, investigating the biological heterogeneity of breast cancer is revealing other exciting developments, for example, in the field of diagnostic imaging. Radiological techniques have a well-established role in each phase of the management of this disease, from screening to monitoring response to medical treatments. Recent MRI modalities allow the simultaneous study of morphology and quantitative functional parameters that are related to the biology of the tumor. Imaging breast cancer biological heterogeneity, which is known to affect prognosis and therapeutic decisions, constitutes a particularly intriguing field of research. For example, dynamic contrast-enhanced MRI parameters are influenced by perfusion abnormalities due to tumor neovascularization. For this reason, this technique has been proposed as a tool to monitor the activity of newer drugs acting on the tumor vasculature [8]. At the same time, a number of studies have suggested that dynamic contrast-enhanced MRI can capture differences in the histopathological and biological characteristics of breast cancer [9–11]. Most of these studies looked at individual histopathological parameters (i.e., tumor grade, proliferation, hormone receptor expression and HER2 status). However, most intriguingly, a study employing MRI to monitor breast cancer response during neoadjuvant chemotherapy showed that the sensitivity of this imaging modality changes according to the different tumor subtypes defined by immunohistochemistry [12]. In this study, MRI was inaccurate at predicting the pathological response in luminal/HER2 negative tumors. Conversely, it showed a significant accuracy in response prediction in triple negative and HER2-positive tumors. A further technological development of MRI techniques is represented by diffusion weighted imaging (DWI). This technique is based on the detection of the thermal energy-induced motion of water

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molecules (Brownian motion). The apparent diffusion coefficient (ADC), a quantitative parameter provided by DWI, is closely related to the cellularity and water content of each different tumor [13]. Due to these functional features, together with the provision of morphological information, DWI is being intensively investigated in the management of breast and other cancers. The differential diagnosis of breast nodules (benign vs malignant) and the ability to capture some histopathological features, such as tumor differentiation, are the major potentialities of this technique [14,15]. Furthermore, ADC is sensitive to precocious variations in the cellular content of a tumor mass in response to treatment [16]. For this reason, DWI is promising as a tool to monitor tumor response during treatment. Recently, in a study involving 190 early breast cancer patients undergoing surgery, we examined ADC variations according to both classical biological factors in immunohistochemically defined breast cancer subtypes [17]. A notable finding was that mean ADC values differed between tumor subtypes. Counterintuitively, higher ADC median values, which are usually considered a feature of benign breast nodules, were found in HER2-enriched and triple negative tumors, whereas the median ADC values were significantly lower in luminal subtypes. Another group has produced similar data observations regarding triple negative tumors [18]. Interestingly, these findings correlate with morphological data obtained via mammography and conventional MRI, indicating that aggressive tumors may display characteristics of benign nodules, such as round shape or regular margins [19]. Capturing the tumor metabolism via MR spectroscopy and PET represents other promising methods of imaging the biology underlying different breast cancer subtypes [20]. The list of examples is becoming long, but all of the newest evidence points to the fact that morphofunctional breast imaging parameters are sensitive to the underlying breast cancer subtype and heterogeneity. A first important conclusion from these experiences is that cutoffs to distinguish benign from malignant breast abnormalities, as well as parameter changes in response to therapy, vary and should therefore be redefined according to breast cancer subtype.

The management of breast cancer from early detection and treatment is undergoing a profound change due to the acknowledgment of its molecular heterogeneity. Consequently, newer imaging techniques that are sensitive to tumor biology open the way to exciting developments in this field and and represent a valuable tool in the pursuit of personalized medicine.

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