Short Communication

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Correlating imaging parameters with molecular data: An integrated approach to improve the management of breast cancer patients

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Abstract

The goal of this review is to provide an overview of the studies aimed at integrating imaging parameters with molecular biomarkers for improving breast cancer patient's diagnosis and prognosis. The use of diagnostic imaging to extract quantitative parameters related to the morphology, metabolism, and functionality of tumors, as well as their correlation with cancer tissue biomarkers is an emerging research topic. Thanks to the development of imaging biobanks and the technological tools required for extraction of imaging parameters including radiomic features, it is possible to integrate imaging markers with genetic data. This new field of study represents the evolution of radiology–pathology correlation from an anatomic–histologic level to a genetic level, which paves new interesting perspectives for breast cancer management.

Keywords

MRI, PET, biomarkers, biobank, radiogenomics

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Introduction

Breast cancer (BC) is the leading death in women worldwide. According to Globocan, in 2018, the estimated number of new cases was 2,088,849, which resulted in the death of 30% of the patients. The risk of developing BC increases with age, with a probability of 2.3% up to the age of 49 (1 in 43 women), 5.4% in the age group 50–69 years (1 out of 18 women) and 4.5% in the age group 70–84 years (1 out of 22 women). BC is a heterogeneous neoplasm, and four BC-molecular subtypes have been defined (Luminal A, Luminal B, HER2 positive, and triple-negative) to help guide treatment decisions. Tumor diagnosis and its classification are traditionally based on histological examination on a biopsy sample. Nevertheless, this approach presents difficulties related to the invasive practice for tissue collection, inter- and intra-observer variability and inability to predict the presence or absence of infiltration in neoplastic lesions. In the last several decades, molecular imaging has developed rapidly in the oncological field and advanced hybrid scanners as positron emission tomography/computed tomography (PET/CT), PET/magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT)/CT, have enhanced the management of oncological patients both for diagnostic and prognostic purposes. As in oncological diagnostic imaging, the intra- and inter-tumor phenotypic heterogeneity is immediately

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evident. In recent years, we have observed a significant increase of studies that aimed to investigate, through a non-invasive diagnostic tool, the use of imaging parameters for predicting tumor behavior, to support histopathological findings, and to predict treatment response.[1] The aim of this review is to provide a concise overview of the studies that integrate imaging parameters with molecular biomarkers for improving each BC patient's diagnosis and prognosis. The final part of this review focusses on the importance of modern biobanks for the individuation of specific diseases biomarkers starting from biological and digital material (i.e. bioimages, data, and metadata).

Correlation among imaging parameters and breast cancer-molecular markers

For a better prediction of tumor malignancy, treatment response and tumor subtypes, many studies have correlated imaging biomarkers extracted from BC primary lesion with immunohistochemical (IHC) markers of BC. The imaging parameters most often analyzed are: perfusion (Ktrans: forward volume transfer constant; Kep: reverse efflux volume transfer constant; Ve: extravascular extracellular space volume; iAUC: incremental blood glucose area under the curve), diffusion (ADC: apparent diffusion coefficient), and metabolic (SUV: standardized uptake value; SUL: lean body mass; MTV: metabolic tumor volume; and TLG: total lesion glycolysis) parameters. Whereas IHC biomarkers to correlate with imaging ones are ER (estrogen receptor), PR (progesterone receptor), HER2, proliferation index (Ki67), and cellular differentiation status (Grade). In these studies, the authors have shown that imaging biomarkers could be used to predict not only BC subtypes,[2] but also pharmacological treatment,[3] to determine the optimal treatment plan,[4] for prognostic purpose,[5] aggressiveness of disease[6] and the presence of metastasis.[7]

In addition to IHC biomarkers, more recently, many research groups have correlated image parameters with coding genes found to be deregulated in BC tissues. Hypoxia-inducible transcription factor-1α (HIF-1α) is a known essential transcription factor involved in regulating metabolic functions, which targets several metabolism-related proteins, and its expression has been associated with breast carcinogenesis and prognosis. Jeong et al.[8] assessed the correlation between HIF-1α and SUV_{max} of ^{18}FDG-PET/CT in patients with invasive ductal BC. SUV_{max} reflected the immunohistochemical expression of HIF-1α and could be used as a good surrogate marker for the prediction of tumor progression in patients with BC. Ahn et al.[9] investigated whether SUV values correlated with the expression of 21-gene that provided a recurrence score (Oncotype DX RS). They found that when SUV_{max} was lower ($SUV_{max(cut\text{-}off)}$ =4) patients were likely to have lower RS (RS⩽26). Recently, Kim at al.[10] provided a mechanistic insight for how the oncogenic miR-155 promotes tumor growth by activating glucose metabolism and regulating critical axis PIK3R1-FOXO3a-cMYC. They found a positive correlation between normalized SUV score and miR-155 levels.

Compared to the aforementioned studies involving PET modality, in recent years the main research efforts have been addressing the relationship between MRI tumor phenotypes and the underlying genetic mechanisms. Ke et al.[11] evaluated the diagnostic efficacy of MRI in combination with the detection of gene expression (Ki-67, BCL11A, FOXC1, HOXD13, PCDHGB7, and Her-2) in BC patients and found that their combination had a higher diagnostic rate (94.5%) than either MRI (81.4%) or gene expression (75.5%) alone. Recently, we performed an exploratory multimodality morpho-functional study in which two circulating miRNAs (miR-125b-5p and miR-143-3p)—able to discriminate BC patients from healthy subjects with high diagnostic accuracy—were correlated with the morpho-functional characteristics of the tumor, as assessed in vivo by PET/MRI).[12] In detail, miR-143-3p showed a strong and significant correlation with the stage of the disease, ADC_{mean}, Kep_{mean}, and SUV_{max}, representing a promising biomarker of tumor aggressiveness. Similarly, miR-125b-5p was correlated with stage and grade 2, but was inversely correlated with $Ktrans_{mean}$ and Ki67, suggesting that this molecule has a potential biomarker of a relatively more favorable prognosis.

Radiogenomics aims to integrate computer-extracted phenotypes from radiological imaging data with genomic data, providing an opportunity to investigate the association between the radiomic tumor features with genomic signature of the same tumor.[1] Mazurowski et al.[13] extracted radiomic phenotypes based on 48 BC tissues and discovered those associated with the luminal B subtype. The relationships between imaging features and gene/protein expression, can also predict patient outcomes, therapy response, and guide personalized medicine. Yamamoto et al.[14] performed a radiogenomic analysis integrating dynamic contrast-enhanced (DCE) MRI with long non-coding RNA (lncRNA) profiling to identify radiogenomic biomarkers of early BC metastasis. Patients with high enhancing rim fraction (ERF) scores were found to experience metastasis earlier than patients with low ERF scores, and the ERF phenotype was strongly associated with eight lncRNAs, including HOTAIR, a known driver of metastasis.[15] Zhu et al.[16] integrated multi-omics molecular data from The Cancer Genome Atlas (TCGA) with MRI data from The Cancer Imaging Archive (TCIA) for 91 breast invasive carcinomas. Quantitative MRI phenotypes of tumors (such as tumor size, shape, margin, and blood flow kinetics) were associated with their corresponding molecular profiles (including DNA mutation, miRNA expression, protein expression, pathway gene expression, and copy number

variation). Authors found that the transcriptional activities of various genetic pathways were positively associated with tumor size, blurred tumor margin, and irregular tumor shape, and that miRNA expression was associated with the tumor size and the enhancement texture. The relationships between imaging phenotypes and gene expression pathways were further elucidated and validated by Yen et al.[17] Quantitative radiomic analysis on 47 invasive BC was performed based on dynamic contrast-enhanced 3 Tesla MR images acquired before surgery and integrated with obtained gene expression data by performing total RNA sequencing on corresponding fresh frozen tissue samples. All radiomic size features were positively associated with multiple replication and proliferation pathways, and were negatively associated with the apoptosis pathway. Interestingly, a diverse array of immune-related pathways showed the most robust relationship with imaging features. As a group, these pathways tended to associate with similar features in the same directionality: tumors with an upregulation of immune signaling pathways, such as T-cell receptor signaling and chemokine signaling, plus extracellular signaling pathways, such as cell adhesion molecule and cytokine-cytokine interactions, were smaller, more spherical, and had a more heterogeneous texture upon contrast enhancement. Tumors with higher expression levels of JAK/STAT and VEGF pathways had more intratumor heterogeneity in image enhancement texture.

Imaging biobanks

The integration of imaging and biological data is an important and active field of research. However, an increasing number of scientific evidence and validation studies are required for translating the experimental results into clinical practice. In this context, we believe that biobanks surely will have a critical role in providing the required biological material. Indeed, biobanks are service units, regulated by international infrastructures (e.g. the Pan-European Biobanking and Biomolecular Resources Research Infrastructure), for collecting and distributing biological material following appropriate scientific, ethical, and legal guidelines.[18] Recently, thanks to the advent of advanced imaging acquisition technologies, a novel category of biobanks arose; that is, imaging biobanks. An example of an imaging biobank is the US-based TCIA,[19] which provides de-identified medical images from cancer patients in DICOM (Digital Imaging and Communication in Medicine file format). The role of imaging biobanks is primarily to provide bioimages for radiomics analysis. Radiomics focuses on evaluating extracted features as novel imaging biomarkers for assessing physiological or pathological processes as well as pharmaceutical responses to a therapeutic intervention.[20] Generally, imaging biomarkers are considered as the expression of bio-signals because they are extracted from the analysis of an electromagnetic, photonic, or acoustic signal emitted by the patient.[20] Consequently, they are not invasive or minimally invasive and could decrease the need for more invasive procedures like biopsy. In this way, imaging biomarkers could be considered as a unique expression of a disease phenotype, and they could be very useful for patient management. The role of imaging biobanks should be focused on the ability to offer data, metadata, raw data, measurements, and biomarkers derived from image analysis to allow feature extraction to be correlated and/or integrated with other disease-related factors (e.g. patient prognosis, pathological findings, genomic profiling, etc.).

Conclusion

The "omics" technologies—such as genomics, transcriptomics, proteomics, metabolomics, and radiogenomics—are improving BC research, with the aims of integrating multiple layers of data for an integrative portrait of BC and realizing precision medicine. Thanks to the development of imaging biobanks and the technological tools required for extraction of imaging parameters, including features (radiomic analyses), it is possible to integrate imaging markers with genetic data. This new field of study represents the evolution of radiology–pathology correlation from an anatomic–histologic level to a genetic level. Imaging features are correlated with genomic data often obtained through high-performance molecular techniques such as NGS technologies, DNA sequencing, and microarray. Radiogenomics can better characterize tumor biology and capture intrinsic tumor heterogeneity with relevant implications for patient care. Existing radiogenomics studies are mainly concerned with oncologic diseases such as glioblastoma multiforme, lung cancer, prostate cancer, and BC. In the future, we could assist in the generation of multi-omics biobanks, where radiomic data could be integrated with genomics, proteomics, or metabolomics findings for an innovative and personalized approach to disease treatment. We believe that imaging biobanks linked to biological samples and patients' clinical information can be considered as a new frontier in biobanking and medical research.

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