6 Imaging Biomarkers and Their Meaning for Molecular Imaging

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Contents

6.1 Introduction

The famous quote from Lord Kelvin "When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarely, in your thoughts advanced to the stage of science" is a really inspiring statement for the explanation of the imaging biomarker concept. Imaging biomarkers can be defined as characteristics extracted from the images of an individual that can be objectively measured and act as indicators of a normal biological process, a disease, or a response to a therapeutic intervention. Biomarkers have been shown to be useful as a complement to the traditional radiological diagnosis to detect a specific disorder or lesion, quantify its biological situation, evaluate its progression, stratify phenotypic abnormalities, and assess the treatment response [1–6].

Despite the evolution of image processing platforms and image quantification solutions to cover unmet clinical needs, their application in daily practice is still work in progress in many aspects. In the field of radiology, a wide variety of algorithms for neuroimaging to be applied to magnetic resonance imaging (MRI) have been developed as well as other solutions for computerized tomography (CT), some of them based on artificial intelligence pipelines, such as lung nodule detection and characterization. Although not being an absolute but a relative quantification, in molecular imaging, the concept of imaging biomarker has been present since the use of standardized uptake value (SUV). Furthermore, workstations and other solutions have been mainly addressed to provide quantitative analysis tools in a patient-specific basis, but not to store

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Fig. 6.1 Stepwise development of imaging biomarkers to convert a clinical idea into value for clinical practice. The AI section refers to the components that can be improved with the use of convolutional neural networks (CNN), image processing, and image analysis steps

quantitative data in databases for the posterior data mining and scientific research in imaging biomarkers. As an example, although the technology is already there [1], today pipelines, like automatically detect the lesions in lymphoma, extract their SUV values as well as their metabolic tumor volume (MTV) and store in a structured report in the PACS are still not available.

In this chapter, we introduce the concept of imaging biomarker and explain the main characteristics of the development process and validation to finally detail how the process can be applied in hybrid modalities where it is highly relevant to combine the spatial information with the functional one.

6.2 Imaging Biomarkers, Paradigm Shift in Medical Imaging

Imaging biomarkers allow to measure subtle tissue changes, either at a structural or at a function level [7]. They are the main enabler of quantitative imaging and the key for the paradigm shift in medical imaging. They can be classified in different types depending on their main application across different clinical scenarios. Imaging biomarkers can be used to extract patient phenotypes, either independently or together with other clinical or genomic variables. The main applications of imaging biomarkers are:

- Detection imaging biomarkers: use as a tool to find high levels of a specific measure in a tissue or organ that can indicate the presence of a disease.
- Diagnostic imaging biomarkers: use as a tool for the identification of the specific disease suffered by the patient.
- Staging imaging biomarkers: use as a tool for grading of the disease severity or extent.
- Predictive/prognostic imaging biomarkers: use as a tool to forecast the progression of the disease and its potential relapse.
- Follow-up imaging biomarkers: use as a tool for monitoring treatment response and disease progression in the patient.

The most supported process for the development of imaging biomarkers, converting a clinical idea or need into clinical value is described in [2] and also proposed in [4], which is divided into different steps (Fig. 6.1).

The first step is the proof of concept, which is usually a small test to solve an unmet clinical need of a specific pathology that can be evaluated with current image acquisition modalities and image processing techniques. The proof of mechanism establishes a link (in magnitude and direction) between the parameter under study and the existence, staging, and evolution of the disease. Thereafter, a design on the most appropriate image acquisition protocol to ensure appropriate image quality is performed; the images needed to

extract the biomarker must be technically adequate (signal-to-noise ratio, spatial resolution, contrast-to-noise ratio, uniformity, among others). The following preprocessing step aims to improve the image quality before the analysis (with techniques such as filtering, interpolation, registration, movement correction, and segmentation). Segmentation is one of the processes that has been significantly improved with the use of artificial intelligence approaches such as the application of convolutional neural networks (CNN). The development of network architectures such as U-Net has permitted the segmentation of organs and structures clearly outperforming traditional computer vision algorithms [8]. The analysis and modeling of the signal is the process by which the quantitative or objective information is extracted from the images. This information can represent structural or functional properties of the tissue. Those imaging biomarkers that can be calculated voxel-wise allow for the representation of the spatial distribution in parametric maps, defined as derived images (secondary) in which the value of a specific parameter is placed as the pixel value. In general, imaging biomarkers have specific measurement units; however, due to the nature of the calculation process, some parameters may be measured in arbitrary units (a.u.). This is the case of radiomics features or parameters such as the fractal dimension. An additional layer of multivariate post-processing applied to the imaging biomarkers allows for the combination of the most relevant features into indicators representing disease status that can be plotted in new parametric images called nosological maps. Measurements of imaging biomarkers in specific lesions or tissues must be optimized to the physiological phenomena under study. A clear example is the conventional approach in the measurements of SUV, consisting of the extraction of the maximum value (SUV_{max}) of the region (instead of average, median, or other histogram descriptors). Automation and AI can allow for the seamless extraction of a wide variety of measurements for a specific imaging biomarker beyond the conventional ones. An exploratory example in molecular imaging that is demonstrating an important evidence with the outcome in lymphoma patients consists of the extraction of metabolic heterogeneity from lesions, beyond the maximum values of SUV, that is, the current standard of care [9]. Finally, after the technical process for the extraction and measurement of the imaging biomarker is clear, a pilot test in the way of a Proof of Principle must be performed in a controlled cohort of subjects to evaluate potential biases related to sex, age, or others. This also serves as a preliminary validation of the method. Comprehensive proofs of efficacy and effectiveness on external, larger, and well-characterized series of subjects will show the ability of a biomarker to really measure (even if it is in a surrogate manner) the clinical endpoint.

6.3 Imaging Biomarkers in Hybrid Molecular Imaging

The imaging biomarkers that can be extracted in molecular imaging are related to the imaging modalities used in the examination. Generally speaking, the imaging biomarkers that can be extracted from the molecular imaging components of the modality (see Table 6.1, considering only those ones based on PET) are the standardized uptake value (SUV), related to the metabolic activity, the metabolic tumor volume (MTV), which is related to the size of the metabolic region within the lesion, the total lesion glycolysis (TLG), derived from the multiplication of the MTV by the average metabolic activity, the delta-, which calculates the difference in a given imaging biomarker between two specific timepoints in the longitudinal course of the disease. Finally, lesion heterogeneity can be characterized both in the anatomical-structural component of the modality, that is, the CT or the MR images, and in the PET component. For the structural or metabolic heterogeneity estimation of lesion, different textural (radiomics) features can be extracted by the use of standard first-order histogram analysis or more advanced second-order techniques: gray level co-occurrence matrix (GLCLM), gray level run-length matrix

Table 6.1 Most relevant imaging biomarkers in molecular imaging, objective of their quantification and specific units

Objective	Modality	Imaging biomarker	Units
Metabolic activity	PET/CT & PET/MR	Standardized uptake value (SUV)	a.u.
Tumoral burden	PET/CT & PET/MR	Metabolic tumor volume (MTV)	mL
Tumoral burden + metabolic activity	PET/CT & PET/MR	Total lesion glycolysis (TLG)	g
Change in metabolic activity	PET/CT & PET/MR	Delta-SUV (ΔSUV), averaged or voxel-wise	a.u.
Lesion heterogeneity	CT, MR, PET/CT, & PET/MR	Textures—radiomics	a.u.

(GLRLM), gray level size zone matrix (GLSZM), gray level dependence matrix (GLDM), neighboring gray tone difference matrix (NGTDM), among others. In total, thousands of descriptors can be obtained, expressing the heterogeneity of a single lesion. Furthermore, these features can be obtained from either a 2D or 3D analysis.

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