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Editorial

Biochemical and imaging biomarkers: the search for the Holy Grail

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Finding disease biomarkers has become, to some extent, the Holy Grail for medical researchers. Biomarkers are parameters that are objectively measured as indicators of normal biological processes, pathological changes, or pharmaceutical responses to a therapeutic intervention (1). Depending on the mode of collecting the information, three types of biomarkers can be distinguished: 1) biochemical or histological parameters detected in tissue samples obtained at biopsy or surgery; 2) biochemical parameters or cells obtained from blood or urine samples; and 3) anatomical, functional or molecular parameters detected with imaging (2). The integration between biomedical imaging techniques and other diagnostic tools, such as biochemical biomarkers, has been advocated as a means for achieving early detection of cancer, and further improvements in diagnostic and therapeutic strategies. Compared with biochemical and histological biomarkers, imaging biomarkers have the advantage of remaining non-invasive and being spatially and temporally resolved. The ability to detect morphological abnormalities in the body by different tools such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) allows for the diagnosis of benign and malignant diseases. However, macroscopic alterations in tissues from disease are often the end result of changes that occurred in a molecular and signaling profile (3). Advances in the field of imaging provide the chance to couple the morphological datasets with functional biological pathways in an attempt to better understand the properties of specific organs in normal and diseased tissue (4). Locating and determining the size of an abnormal growth in one tissue might only reflect benign disease, and the lack of need for medical intervention. In addition, knowing the size and location of a particular abnormal tissue would provide little or no information regarding proper treatment strategies and subsequent response to therapy. As a consequence, imaging biomarkers are now playing an increasing role in tumour diagnosis, work-up and response to therapy (5, 6).

Imaging biomarkers are to a large extent based on nuclear imaging technologies, such as scintigraphy, single-photon emission tomography (SPET) and positron emission tomography (PET) (7). The advantage of these techniques is the high level of sensitivity for detecting subtle biological changes using limited quantities of the imaging agent (i.e., radiopharmaceuticals), and non-invasive approaches.

Molecular imaging and, particularly, nuclear medicine procedures, are characterized by very high sensitivity and, consequently, a very high negative predictive value (8). Early diagnosis or exclusion of infection and inflammation is of the utmost importance for the optimal management of cancer patients. The enhanced uptake of ^{18}F-fluorodeoxyglucose (FDG) in activated inflammatory cells, such as lymphocytes or macrophages is related to significantly increased levels of glycolysis as a result of increased numbers of cell surface glucose transporters, particularly after cellular stimulation by multiple cytokines (9).

Therefore, in recent years PET or PET/CT has been proposed as a diagnostic tool in settings where the detection or characterization of infection or inflammation is the main focus of investigation (10). Additionally, FDG-PET or PET/CT may differentiate between malignant and inflammatory processes in settings where such a distinction is essential for optimal patient management. This is due to the observation that standardized uptake values (SUVs) of inflammatory and non-neoplastic lesions tend to remain stable or decrease, while those of malignant lesions tend to increase over time (11).

In this issue of the *Journal*, an interesting paper by Giovanella and colleagues describes the specificity of serum procalcitonin (PCT) in a large cohort of patients with different solid carcinomas (12). The diagnostic performance of this biochemical biomarker was evaluated using FDG-PET/CT as the ''gold standard'' in the detection of infectious and inflammatory diseases, other than glucose-avid carcinomas. Their data proved that solid carcinomas, ''per se'', did not increase circulating PCT concentrations, regardless of the histotype and the stage of disease.

The performance of a diagnostic test is routinely evaluated from estimates of diagnostic sensitivity and specificity, construction of receiver-operating characteristic (ROC) curves and additional estimates of negative and positive predictive value and likelihood ratios. Valid estimates of diagnostic specificity require sizable groups of subjects; all of whom must be correctly identified according to the absence of disease by methods other than the diagnostic tests being evaluated. However, it should be underlined that the comparison method does not always possess the characteristics of a true ''gold standard''. The present study suggests that molecular imaging procedures may be in the perfect position to exclude disease, even when at subclinical levels in the ''control'' population, thus contributing to better define the ''specificity'' of a diagnostic marker. Further studies and research is

needed to explore the integration between laboratory and imaging information, and its contribution to more effective validation of circulating biomarkers.

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