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Molecular Imaging and Biomarkers: A Bidirectional Way

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Medical imaging is one of the fastest growing areas in medicine and, within it, molecular imaging (MI) is an example of dynamic change and adaptation to technology and future. According to Society of Nuclear Medicine and Molecular Imaging, Molecular Imaging is *"the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems".* MI is intimately tied to the biology of the disease and shows a new bidirectional way: biology *to* imaging *vs.* imaging to biology. The main goal of MI is to search and define specific targets (biomarkers) of a given disease in order to obtain new tracers and therapies, being the final result the prevention and the diagnostic-therapeutic individualization (personalized medicine), required nowadays. In the past, biomarkers have been used preferently to distinguish both normal and pathological (malignant and non malignant) conditions, but now new roles are coming, as those to define the outcome of patients, to develop new therapies and to design new preventive actions [1].

MI plays an important role in all stages of cancer management and the use of biomarkers is critical to achieve excellent results. A few years ago, Hananhan and Weinberg [2] defined the so-called: hallmarks of cancers, which comprised six biological capabilities acquired during the multistep development of human tumors. Later [3] they included two emerging hallmarks more: reprogramming of energy metabolism and avoiding immune destruction, in particular by T and B lymphocytes, macrophages and natural killer cells, as well as two enabling characteristics: genome instability and mutation, and tumor-promoting inflammation. In our context, the most important hallmark is the reprogramming of cellular energy metabolism, in order to obtain the sufficient energy and to support cell growth. Several biochemical pathways are involved, but we want emphasize on the oxidative stress, because malignant cells use oxidative environment to promote tumor progression and because it underlies many of the hallmarks. So, Reactive Oxygen Species (ROS) are involved in Warburg effect, up-regulation of glucose transporter, activation of some oncogenes (ras, myc), mutation of p53 and increase of HIF-1 linked to hypoxia [4].

Positron emission tomography (PET) is a non-invasive nuclear medicine diagnostic imaging procedure, using positron emitting radiotracers, widely used in clinical practice. It is a molecular imaging procedure which detects, quantifies and characterizes different biological targets. At present, the procedure includes PET and CT data in the same imaging session and allows accurate anatomical localization of the biological lesions detected on the PET scan. For this reason, PET/CT is the fastest-growing imaging modality used worldwide. There are a lot of radiotracers, being fluorine-18-fluoro-D-glucose (^{18}F-FDG) the most used in daily practice, an analogue of glucose that provides valuable functional information based on the increased glucose uptake by cancer cells. This uptake can be quantified by means of the maximum standardized uptake value (max SUV), a semi-quantitative measure, widely used in the daily praxis. Standardized uptake value (SUV) measurement can be influenced by a variety of technologic (scanner and reconstruction parameters), *clinical and biologic factors (biomarkers)*. In pulmonary pleomorphic carcinoma, maxSUV positively correlated with GLUT-1, GLUT-3 (glucose metabolism), VEGF and microvessel density (angiogenesis). In non small cell lung carcinomas (NSCLC), FDG uptake was significantly higher in squamous cell carcinomas compared with other

histological subtypes, whereas it was lower in bronchoalveolar tumors. The glucose accumulation depended on GLUT-1, GLUT-3 expression and tumor differentiation. Oligodendroglial tumors had higher uptake values than astrocytomas, whereas in squamous cell carcinoma of the head and neck, a high uptake of ^{18}F-FDG is linked to an aggressive phenotype associated with p53 expression and VEGF. In non-small cell lung carcinomas, FDG uptake was associated with some genes (LY6E, RNF149, MCM6, FAP) linked to survival and higher maxSUV values were noted in HER2+ and basal breast tumors and the percentage variation of the standard uptake values (retention index) was positive and significantly related with hormone-independence and Ki67 index. Likewise, in HER2-overexpression breast cancer maxSUV was useful after two cycles of chemotherapy to predict residual disease and outcome. FDG uptake can be also useful for predicting some genetic alterations in tumors; so, FDG uptake was higher in colorectal carcinomas with KRAS/BRAF mutations, and the KRAS status could be predicted with an accuracy of 75% when the maxSUV cut-off of 13 or 14 was used [5]. Also TP53 mutations were associated with high SUV values, and the accuracy of maxSUV greater than 10 in predicting that mutation, was 60% [6].

In lung adenocarcinoma higher maxSUV values are more likely to carry EGFR mutations after multivariate analysis [7], but other groups have not been proven. In our experience the presence of mutations in exon 19 of the EGFR gene is associated with higher maxSUV value, reflecting a great tumor metabolism and better response to tyrosine Kinase Inhibitors. These results extrapolate that 18FDG uptake might be helpful to discriminate patients who harbor EGFR mutations, especially when a genetic test is not feasible. In the same direction, we founded that SUV values are related with both EGFR mutations and cellular Glucose transporters expression (GLUT1-2, SGLT1-2), showing that those values for clinical purposes should be used carefully and MUST take into account the biological, physiological, metabolic and genetic profiles of the tumor cell. Other parameters related with glucose uptake by tumor cells and used in clinical practice are peak SUV, metabolic tumor volume (MTV), and total lesion glycolysis (TLG).

Molecular imaging is evidencing a new feature of great importance: the intratumoral metabolic heterogeneity which seems to be related to histopathological and biological features (hormoneindependence, proliferation, histological grade, subtype…, etc.) in different tumors. Chicklore et al, stated in his paper that *"The medical images contain more useful information than may be perceived with the naked eye, leading to the field of radiomics, whereby additional features can be extracted by computational post-processing techniques"* [8]. A new fact is the *texture analysis* of radiological images which reflects the spatial variation and heterogeneity of a tumor. Orlhac et al. [9] studied 31 texture indices, 5 first-order statistics (histogram indices) derived from the gray-levels histogram of the tumor region, and observed that three histogram indices were highly correlated with SUV, and 4 texture indices were correlated with metabolic volume. Dong et al. [10] analyzed the textural features (entropy and energy) of the three-dimensional images using MATLAB software and observed significant correlations of both parameters with T stage, maxSUV and N-stage in patients with esophageal squamous carcimoma. Likewise, entropy was useful for detecting carcinomas above stage II. Similar conclusions were reported recently with MRI technique in patients with glioblastomas or CT in adenocarcimas of the lung with or without EGFR mutations or in PET/MRI studies. Sometimes, heterogeneity quantification is associated with metabolic volume in order to obtain a prognostic parameter in some carcinomas [11]. Nevertheless, the need for standardized methodology in tumor texture analysis is necessary.

This close and bidirectional relationship between molecular imagining and biomarkers has been described also in processes associated with radiation therapy. Thus, in its editorial, West et al. [12], argue that the radiotherapy-related research community has been measuring biology over 50 years focused on tumor and normal tissue radiosensitivity, tumor proliferation and tumor hypoxia, all of them very specific for radiotherapy. Radiation treatments need to exploit biological information. Such personalized precision radiotherapy requires of the narrow and organized synergy between biomarkers and molecular imaging-based planning.

But biomarkers will not only help us to choose the most appropriate imaging technique to study the disease, but images itself are going to define some (and crucial) biological facts. Also, certain biomarkers and certain images are choosing us the correct therapeutic protocol and help to assess its effectiveness. Therefore, the challenge is to find more specific and more sensitive biomarkers that allow this early diagnosis, biological characterization of a particular process, specific diagnosis, and the establishment of a personalized therapy, at both, pharmacological and radiotherapy levels. The desired individualization is a mandatory requirement.

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