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Review

PET/MRI: Multiparametric imaging of brain tumors

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ABSTRACT

A combination of morphological imaging of the brain with microstructural and functional imaging provides a comprehensive overview of the properties of individual tissues. While diffusion weighted imaging provides information about tissue cellularity, spectroscopic imaging allows us to evaluate the integrity of neurons and possible anaerobic glycolysis during tumor hypoxia, in addition to the presence of accelerated synthesis or degradation of cellular membranes; on the other hand, PET metabolic imaging is used to evaluate major metabolic pathways, determining the overall extent of the tumor (^{18}F-FET, ^{18}F-FDOPA, ^{18}F-FCH) or the degree of differentiation (^{18}F-FDG, ^{18}F-FLT, ^{18}F-FDOPA and ^{18}F-FET). Multi-parameter analysis of tissue characteristics and determination of the phenotype of the tumor tissue is a natural advantage of PET/MRI scanning. The disadvantages are higher cost and limited availability in all centers with neuro-oncology surgery. PET/MRI scanning of brain tumors is one of the most promising indications since the earliest experiments with integrated PET/MRI imaging systems, and along with hybrid imaging of neurodegenerative diseases, represent a new direction in the development of neuroradiology on the path towards comprehensive imaging at the molecular level.

1. Introduction

The brain, as the most metabolically active tissue of the human body, is characterized by its variable behavior and often overlapping changes at the metabolic, structural and functional levels. Considering the brain either in structural or functional terms only is inadequate in assessing the pathophysiological chain of cause and effect. In contemporary medicine, diseases of the central nervous system are one of the most important challenges of diagnostic imaging. The guiding principle is multiparametric imaging and multifactorial analysis of the tumor phenotype [1]. A combination of morphologic, metabolic, microstructural and functional approaches to imaging is currently optimally enabled by combining positron emission tomography with magnetic resonance imaging.

The population incidence of brain tumors has had a growing trend since 1970s to 1990s [2]. In the western population, the number of patients with neuroepithelial tumors is being steadily the important cause of cancer-based mortality [3]. Histological type, the level of differentiation and the possibility to perform radical removal of the tumor are the most important factors for the prognosis of patients. Therefore, there have been increasing demands on preoperative imaging of the tumor tissue itself, determination of the overall extent of the disease and assessment of the location to collect a biopsy sample for histological diagnosis. In addition to assessing the tumor itself, it is very important to visualize the relationship of the tumor process to the functional centers and white matter tracts. In patients who have already undergone surgical resection or have received a combination of chemotherapy and radiotherapy, it is important to evaluate the presence of residual tumor tissue, recognize potential changes in tissue behavior, secondary changes in the brain tissue related to the presence of radionecrosis and other non-tumor reparative processes after the treatment. Magnetic resonance imaging has been the gold standard for neuro-oncology diagnosis, where functional and multiparametric imaging have their role in advanced imaging algorithms [4].

2. Patient preparation and data acquisition

The basic requirement in the preparation of patients before PET/MRI scanning is accumulation of the radiopharmaceutical under resting basal conditions. The patient should be placed on bed

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resting, preferably in a darkened room in silence. The time of radiopharmaceutical accumulation varies between different substances. In addition to general measures during the accumulation of the substances, it is also important to adhere to fasting requirements in patients. This is particularly important when using ^{18}F FDG, which features a significant competition with glucose. Therefore, at least four hours of fasting are required prior to its administration. For other substances, fasting has limited importance in influencing the accumulation of substances, but fasting can minimize the risks associated with the development of nausea during the examination.

PET brain scanning is performed using an integrated scanner with a PET detector insert made of lutetium silicate. The acquisition itself is performed with simultaneous PET and MRI scanning in the magnetic resonance head coil with twelve receiving channels. The first step is the localization scan. The localization is followed by a T1-weighted sequence of VIBE two-point-Dixon gradient echo. The obtained in-phase, opposed-phase images, and calculated fat-images and water-images are used to create a tissue model for attenuation correction and subsequently to reconstruct the attenuation-corrected PET images. The initial sequence is followed by PET data acquisition. PET images are used to evaluate the metabolic processes in the brain tissue based on data usually acquired during the 15–20 min of continuous PET data acquisition. However, data can also be acquired dynamically on a continuous time axis from intravenous and development of the time dependency of the radiopharmaceutical accumulation monitored. Dynamic examinations require long data acquisition, typically from 20 to 40 min, and the acquisition starts with the beginning of the actual administration of the radiopharmaceutical. For radiopharmaceuticals with a dual distribution pattern, i.e., perfusion-dependent distribution and late tissue-specific steady-state distribution, biphasic acquisition is a possible variant.

Being located in the neurocranium, the brain is a tissue without independent distinctive movements that would lead to distortion of spatial information or distortion of the space. However, precise assessment of the metabolic activity of the gray and white matters has revealed that pulsating movements of the brain tissue cause an impairment of the spatial resolution of PET scan with a "blurred" activity. These problems could be solved using segmented motion-correction reconstruction [4]. At present, the data acquisition by echoplanar BOLD (blood-oxygen-level-dependent) is used to segment PET data and to correct this type of artifact (COMPASS, Siemens Healthcare).

3. Brain MRI

Standard protocol using T2-weighted sequences of fast spin-echo, T2-weighted FLAIR (fluid attenuation inversion recovery) sequences, diffuse imaging using echoplanar sequences with calculation of the map of apparent diffuse coefficient (ADC) and T1-weighted gradient echo sequences (FLASH – fast low angle shot single or MPRAGE – magnetization prepared rapid gradient echo) is used for structural imaging in PET/MRI scans of the brain. Detailed macrostructural morphological imaging still brings basic and pivotal information. Susceptibility weighted imaging (SWI) is an advantageous tool to visualize the deposits of hemoglobin degradation products, which benefits from extreme changes in T2* signals for hemosiderin and deoxyhemoglobin and can be used to detect signs of bleeding.

Many studies suggest a positive correlation between the histologically established grade of glial tumor and diffusion restriction, which means a negative correlation between tumor grade and the value of the apparent diffusion coefficient (ADC) [6], the diffusion restriction also being an important feature of brain lymphomas. Diffusion-weighted imaging in the primary diagnosis significantly contributes to finding tumors of small dimensions, and increases sensitivity and specificity in the detection and differential diagnosis of brain tumors [6].

Since a PET/MRI scan of the brain is usually performed in patients for whom information on the structure and level of organization of the brain's white matter in the surrounding of the tumor tissue may be significant, the standard diffusion weighing sequence can be replaced in the imaging protocol with multidirectional diffusion weighted imaging (MDDWI). The collected data can be used to calculate the diffusion trace imaging, apparent diffusion coefficient (ADC), fractional anisotropy (FA) and diffusion tensor with the option of tractography reconstruction. Fractional anisotropy maps are important in distinguishing an expansive type of growth, when increased organization and anisotropy are paradoxically observed in the white matter around the tumor tissue, and on the contrary, decreased fractional anisotropy is seen at the site of white matter disorganization caused by infiltrative tumor growth and/or vasogenic edema.

4. Tissue perfusion and extracellular molecular exchange

During extracellular distribution, most substances follow similar behavioral principles. Gadolinium chelates are model substances traditionally used to visualize the integrity of the blood-brain barrier. Although conventional perfusion models of brain tissue magnetic resonance imaging use the T2 effect of the gadolinium contrast agent and echoplanar sequences, gradient echo sequences with rapid acquisition time can be used to obtain a set of images in the range up to steady distribution, which can be used to better evaluate and quantify certain pharmacodynamic parameters important for evaluation of the tumor tissue. It is now possible to use T1-weighted spoiled-gradient-echo VIBE (Volume Interpolated Breath Hold Examination) sequences with the acquisition of 20–30 series in the first minutes from the time of intravenous contrast medium administration with continuous acquisitions one after the other, or using overlapping data acquisition TWIST, TWIST-VIBE and the like. Standardized contrast agent administration using an automatic injector is essential for subsequent image analysis. Gadolinium contrast agent is administered at a dose of 0.1 mmol/kg body weight at 1.5–2 mL/sec and flushed with 50 mL normal saline. A contrast agent with a higher concentration (one-molar gadobutrol) or higher relaxivity (gadobenate dimeglumine) may be preferable to achieve higher changes in signal intensity over time with a steeper bolus curve.

Movement of circulating fluid in the tissue depends on a number of interrelated processes [6,7]. Primarily, these are blood supply to the tissue, which means inflow through the arterial bloodstream and flow through the capillaries, while another important parameter is the exchange of fluid between the intravascular extracellular and extravascular extracellular space (i.e., between the blood plasma and tissue fluid), depending on the permeability of the vascular wall, the volume of the extravascular extracellular space and its microstructure (stroma). The essential and simplest expression of the dynamic phenomenon is visualization of the saturation curve, either as relative values or using mathematical models, as the calculated concentration of the administered contrast agent (specification of the contrast agent is required, particularly with regard to the size of the molecule). The steepness of the concentration increase of the contrast agent indicates the state of tissue vascularization, but is also suitable for comparative examinations before and after the treatment.

In addition to evaluating the shape of the curve, it may be helpful to use semi-quantitative numerical parameters or their color-coded maps for the evaluation, such as the integral of the initial area