Multimodality-multiparametric brain tumors evaluation

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Abstract
Brain tumors represent a vast group of lesions, originating from different neuronal cells with different degrees of aggressiveness. Despite some technological advances either pre or post-treatment, these tumors may share similar imaging findings and properties, rendering diagnosis/prognosis, an ambiguous process. Gadolinium-enhanced magnetic resonance imaging remains the gold standard for providing detailed morphologic information, but presents several limitations due to the overlap of findings, in cases such as progressive tumor and post-radiation related effects. Tumor cellularity, vascularity, proliferative activity, metabolic and functional profiles are a few of many characteristics that may further support tumor classification, but cannot be assessed by conventional imaging alone. We review the aforementioned factors and indicate how they improve tumor characterization and grading in order to design the optimal treatment strategy and better evaluate post treatment efficacy

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Introduction

Accurate diagnosis and treatment evaluation of cerebral lesions as well as patients' management are the primary concerns in Neuro-oncology. Over the last decades, there has been a rapid evolution in the detection of structural abnormalities, localization and assessment of the extent of the lesion, using morphological imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI). Advanced MRI techniques, including diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), dynamic-susceptibility contrast imaging (DSCI) and magnetic resonance spectroscopy (MRS), provide additional insight to tissue microstructure, perfusion and metabolism respectively. However, these techniques still face limitations in the evaluation of cell proliferation and therefore in the identification of tumor grade, treatment-induced changes or recurrences.

Single photon emission tomography (SPET) and positron emission tomography (PET) evaluate functional/molecular profiles of the brain. Contrary to conventional MRI, these techniques may provide information on proliferative activity and metabolic features of brain tumors. Visualizing molecular tracers and assessing cell metabolism and receptor status, SPET and PET can complement conventional and advanced imaging methods, to establish a noninvasive histological diagnosis prior to operation, to distinguish between residual or recurrent viable tumor and scar tissue and to estimate treatment response at the postsurgical and post-radiation stage.

In this paper we aim to briefly discuss how the multiparametric data derived from these imaging modalities can optimize clinical diagnosis and prognosis.

Advanced MRI techniques

Conventional MRI is essential for the assessment of structural changes in the brain, due to its high soft-tissue contrast and resolution. Despite its excellent soft tissue visualization and the variety of imaging sequences, conventional MRI presents limitations regarding certain tumor properties, such as tumor vascularity, cellularity and metabolism.

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging method that exp-

lores particular chemical compounds or metabolites, providing an in-vivo biochemical profile of the tissues [1]. Proton-magnetic resonacne spectroscopy (1H-MRS) yields a collection of peaks at various radiofrequencies, representing proton nuclei in different chemical environments, which are displayed as a spectrum. The brain is an ideal area for the application of ^{1}H-MRS, due to its relative homogeneity and lack of involuntary movement. All metabolites have been related to specific histological features [2]. Taking into account that brain tumor histology varies, from relatively benign primary brain lesions (e.g., astrocytomas) to more malignant grades (anaplastic astrocytomas, glioblastomas), this variation can be reflected into the concentration of metabolites.

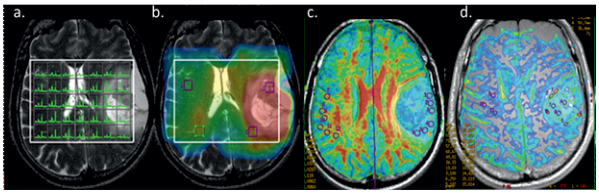

Figure 1. Advanced MRI techniques. a) 2D Magnetic Resonance Spectroscopy, b) Metabolite Mapping, c) Diffusion Imaging, d) Dynamic Susceptibility Contrast Imaging.

Diffusion is the result of random water movement and it occurs at equal rates in all directions inside an isotropic medium. In a much more complex environment, such as the human brain, water motion is restricted by natural intracellular (neurofilaments and organelles) and extracellular (glial cells and myelin sheaths) barriers that impede free diffusion. Specifically, water molecules diffuse mainly along the direction of white matter axons, rather than perpendicular to them [3]. Diffusion-weighted imaging (DWI), exploits this physical process to acquire images considering water diffusion as isotropic, which can be quantified by the apparent diffusion coefficient (ADC). Diffusion tensor imaging (DTI) uses this preferential water diffusion to image the brain. Fractional anisotropy (FA) is one of the indices derived from DTI, which describes the degree of water directionality inside a voxel [4]. Apart from describing water diffusion properties in the brain, ADC and FA have been correlated to tissue cellularity. Regarding brain tumors, studies have shown that ADC and FA may be considered as indices of cell density, contributing in noninvasive tumor grading [5].

Dynamic-susceptibility contrast imaging (DSCI), enables the non-invasive qualitative and quantitative assessment of dynamic perfusion in tissues, through the administration of gadolinium-based contrast agents [6]. Dynamic-susceptibility contrast imaging (DSCI) utilizes very rapid imaging to capture the first pass of the intravenously injected contrast agent and to measure tissue microcirculation. As the paramagnetic contrast agent passes through the vasculature, signal intensity changes over time, which is illustrated on the signal intensity-time curve. Generally, increased tumor vascularity and neo-angiogenesis have been related to malignancy; however this may not always be the case. Nevertheless, the ability to non-invasively quantify vascularity and neovascular proliferation renders DSCI an important diagnostic tool that can complement conventional imaging.

Nuclear medicine imaging modalities

As mentioned previously, the proliferative activity and metabolic features of cerebral tumors cannot be assessed by morphologic imaging alone. Single photon emission tomography (SPET) and positron emission tomography (PET) have been widely used to evaluate brain functionality on a molecular and cellular level, by measuring the radiotracer uptake.

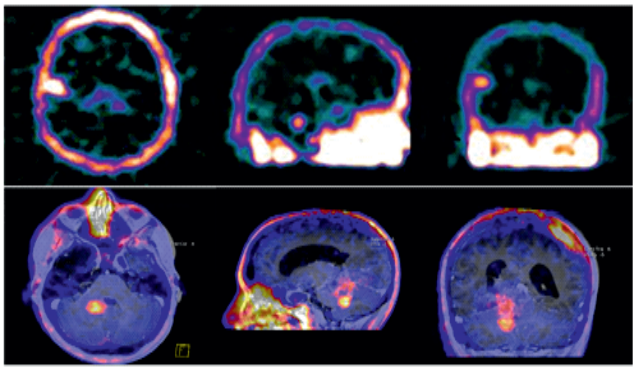

Figure 2. Nuclear Medicine techniques: a) Brain SPET (from the University Hospital of Larissa), b) Brain PET, fused with MRI (courtesy of V. Prassopoulos, PET-CT Department, Hygeia Hospital, Athens).

Even though SPET presents lower spatial resolution compared to PET, it is considered a credible imaging alternative, combining both lower cost and wider availability [7]. Thallium-201 (^{201}Tl) was initially introduced as a myocardial perfusion imaging agent, but soon after researchers investigated its potential as a neuro-oncological tracer [8-11]. As an alterna-tive to ^{201}Tl, technetium-99m (^{99m}Tc)-labelled compounds have also been used to evaluate brain tumors metabolism [11]. Their use is advantageous over ^{201}Tl, due to the 140keV gamma ray energy, high photon flux, higher spatial resolution, less radiation burden to the patient and excellent availability [12]. ^{99m}Tc-methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin (^{99m}Tc-TF) passively concentrate significantly in mitochondria and are markers of cellular transmembrane electrical potentials [13]. Given that tumor cells present higher mitochondrial density as well as higher transmembrane electrical potential than the surrounding tissue, these radiopharmaceuticals accumulate more intensely in tumor cells, and consequently in malignant tumors as tumor-seeking agents [14]. The additive diagnostic value of both ^{99m}Tc-labeled compounds has been extensively evaluated in brain imaging [13-15]. Previous reports, demonstrated a strong positive correlation of the agent uptake to neoplastic proliferation, suggesting that ^{99m}Tc-MIBI and ^{99m}Tc-TF may aid in tumor diagnosis [13]. Hence, the advances in gamma-emitting radiopharmaceuticals have contributed to a better understanding of brain tumor metabolism and to an overall improvement of diagnostic and prognostic accuracy [16].

Moreover, studies have shown that the ability of PET imaging to detect functional and metabolic abnormalities in the brain makes PET a strong tool for tumor characterization, grading and for post-treatment follow-up [17].

The radiopharmaceuticals used for PET represent the principal agents for molecular imaging as they in-vivo label biochemical processes and metabolic pathways (particularly glycolysis, protein/DNA synthesis). Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is the most widely used PET tracer for brain imaging, due to its relatively long half-life (110min) that enables the distribution from a central cyclotron to nearby sites and to the distinction between residual tumor and radiation-induced changes and staging [18-19]. Nevertheless, the high glucose metabolism in normal brain parenchyma may hinder the accurate delineation of brain tumors or may decrease diagnostic sensitivity in cases such as differentiation of low-grade lesions from non-neoplastic diseases (e.g. inflammations) that may also show ^{18}F-FDG uptake [20-21]. To overcome ^{18}F-FDG drawbacks, amino acid PET radiotracers have been introduced. Their main advantage over ^{18}F-FDG in brain imaging is the significantly higher sensitivity in detecting viable tumor tissue [22]. Neoplastic cells show higher amino acid uptake, due to the increased amino acid transport and protein synthesis in malignancies, contrary to the low uptake in the normal brain parenchyma [23]. A number of studies have investigated the use of ^{11}C-methionine (^{11}C-MET) for brain imaging, due to its convenient radiochemical production. Even though previous reports showed that ^{11}C-MET may be useful to visualize lesions (e.g. low-grade glioma) not detected by ^{18}F-FDG, its short physical half-life (20min) restricts its clinical use [24]. Therefore, novel ^{18}F-labeled amino acid PET tracers, who share similar properties as ^{11}C-MET, have been introduced to assess brain metabolism. Additional PET tracers, ^{18}F-fluoromisonidazole (^{18}F-FMISO) and ^{18}F-fluoroazomycin-arabinoside (^{18}F-FAZA) for hypoxia imaging and ^{18}F-fluorothymidine (^{18}F-FLT) for tumor proliferation have been developed and clinically validated, allowing a better metabolic evaluation and a cost-effective application.

Multimodal imaging in neuro-oncology

Multimodality imaging has been proposed as a more powerful tool to assess brain abnormalities and evaluate treatment strategies [25]. Towards this direction, a relatively limited number of studies have examined the contribution of multimodal brain tumor imaging (advanced MRI and SPET/PET) and the diagnostic value of multiparametric data analysis [26-28].

Differential diagnosis

Many non-neoplastic lesions such as brain abscess, inflammatory lesions, infarctions, hematomas, and demyelinating diseases can mimic brain neoplasms such as glioma, metastasis, and lymphoma, on neuroimaging, while several intracranial tumors can present in the absence of typical space-occupying lesions, rendering the differential diagnosis a challenging process [29]. Contrast MRI can provide detailed morphological information and the combination of advanced MRI techniques and PET/SPET modalities can supply additional insights into lesions metabolism, proliferation rate, invasiveness, and interaction with surrounding tissues [30]. These insights may prove useful in differential diagnosis of neoplastic vs non-neoplastic lesions and thus optimize the therapeutic decision-making and surgical outcome.

Glioma grading

Gliomas represent the most common cerebral tumors and the preoperative assessment of their grade is important for therapeutic decision-making. Low-grade gliomas (LGG) (grades I and II) progress slowly over time and are usually benign. Depending on their cell origin they may be termed as oligodendrogliomas, astrocytomas or of mixed type [31]. High-grade gliomas (HGG) (grades III and IV) are considered malignant.

The diagnostic value of single imaging modality (either SPET/PET or advanced MRI) in glioma grading has been extensively investigated in the past years. Significant differences in water diffusion, apparent diffusion coefficient (ADC) and directionality, fractional anisotropy (FA) have been observed between LGG and HGG and the related diffusion parameters have also shown correlation to tumor cell density [32-34]. Regarding dynamic perfusion, rCBV has been reported as a strong index of differentiation-especially in the peritumoral areas of the lesions–increasing with higher glioma grades and being significantly related to tumor vascularity. In terms of MRS, choline/creatine (Cho/Cr) and choline-N-acetylasparic acid (Cho/NAA) ratios are significantly different between LGG and HGG, and these differences become more dominant in the peritumoral area [35]. Furthermore, studies on SPET and PET radiotracer uptake have reported that higher uptake is usually indicative of malignant glioma grades [36-37]. Nevertheless, the diagnostic contribution of single imaging modality for glioma grading still remains controversial. Overlapping of diffusion, perfusion and spectroscopic values has been observed between LGG and HGG, most probably because gliomas comprise a relatively heterogeneous group of tumors [38]. Additionally, not all SPET/PET radiopharmaceuticals are grade-specific or suitable to assess tumor recurrence from radiation necrosis [39]. Hence, research interest has been shifted towards the additive diagnostic value of multimodal imaging for glioma assessment, examining various combinations of SPET or PET tracers with advanced MRI techniques.

Post-treatment evaluation of tumors

Current standard treatment care for newly diagnosed malignant tumors includes a combination of surgery, postoperative adjuvant radiation therapy and chemotherapy, depending mainly on tumor histology and location. While these therapies are effective for treating gliomas, their efficacy has led to an increase in treatment induced tissue necrosis and thus pseudo-progression of the tumor [40]. Accurate diagnosis of these post-treatment lesions as either tumor recurrence or treatment effects is a frequent challenge in neuro-oncologic imaging, important to determine prognosis but cannot be answered by contrast-enhanced MRI alone. Changes in contrast enhancement MRI can be induced by a variety of non-neoplastic processes, such as treatment-related

inflammation, postsurgical changes, ischemia, subacute radiation effects and radiation necrosis [41].

Advanced MRI techniques have been extensively investigated to quantify the treatment response and the extent of residual tumor as well as to differentiate recurrent tumor growth from treatment-induced tissue changes, such as radiation necrosis [42]. Alterations in brain metabolites can be assessed by MR spectroscopy; the presence of lipid-lactate complexes and decrease in other metabolites including choline, indicate radiation necrosis. However, both pseudo-progression and true disease progression may present similar metabolites alterations due to neuronal loss, abnormal cellular membrane integrity and anaerobic metabolism [41]. In addition, radiation necrosis presents higher ADC values (low cellularity) compared to tumor progression (high cellularity), while tumor recurrence presents lower ADC ratio and higher FA values compared to necrosis [43]. Tumor perfusion assessed using MRI, and particularly relative cerebral blood volume (rCBV) ratio, which is an essential biomarker of angiogenesis, significantly higher in tumor recurrence than in radiation-necrosis [44]. Nevertheless, these findings often overlap as recurrent and necrotic tumor may co-exist. In terms of Nuclear Medicine, PET and SPET radiopharmaceuticals have also been investigated in distinguishing tumor progression from treatment-related changes but they suffer from several limitations, like benign lesions with high glucose uptake mimicking tumor recurrence, low spatial resolution etc. [45]. Therefore, the use of multiple functional imaging techniques is expected to lessen the chance of lesion misinterpretation as every single imaging modality gives additional information. Figure 3 summarizes all imaging modalities discussed, with their approximate sensitivities and specificities as they currently stand regarding multimodal brain tumor evaluation. Of course, radiation burden should always be considered.

In conclusion, neuro-imaging has evolved from a purely anatomy-based specialty to a multi-parametric discipline that can diagnose morphologic abnormalities, hemodynamics, intra-cellular microstructures and cellular metabolism. The combination of conventional and advanced MRI techniques along with Nuclear Medicine modalities will play a significant role in the diagnosis of intracranial lesions in the future.

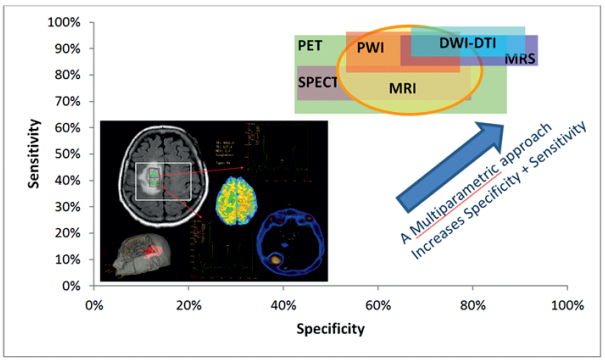

Figure 3. Summary of the approximate range of sensitivities and specificities of all the imaging modalities discussed in this work. It is evident that multiparametric evaluation is expected to increase sensitivity and specificity of brain tumor diagnostic imaging.

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