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Review

An Overview of Advanced Multimodal Imaging Techniques in Low Grade Gliomas

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REZUMAT

O privire de ansamblu asupra tehnicilor imagistice multimodale avansate în glioamele slab diferențiate

Date generale: Neuroimagistica joacă un rol cheie în diagnosticul și managementul glioamelor slab diferențiate. O evaluare extinsă și noninvazivă a localizării, metabolismului și ratei de proliferare a tumorii, a gradului său de invazie și interacțiunilor cu țesuturile învecinate, precum și răspunsul său la tratament și identificarea precoce a recurențelor este foarte utilă în managementul clinic.

Metode: Autorii au evaluat studiile publicate în literatura de specialitate (Medline și Cochrane Library până la data elaborării acestui articol) și au încercat să determine cel mai bun algoritm de management neuroimagistic pentru glioamele slab diferențiate, precum și cum pot fi îmbunătățite strategia chirurgicală, rezultatele globale și calitatea vieții pacienților.

Rezultate și concluzii: Utilizarea protocoalelor RMN și PET poate contribui substanțial la confirmarea unui diagnostic (deși biopsia nu trebuie niciodată exclusă), furnizând încă de la început informații asupra prognosticului și permițând stabilirea unor protocoale individuale de management terapeutic corecte. Aceste tehnici contribuie de asemenea la planificarea parcursului chirurgical, identificarea segmentelor cele mai active din tumorăși a extensiei tumorii. Efectuarea simultană a RMN și PET în aceeași ședința cu ajutorul unui aparat hibrid este presupusă a îmbunătăți atât diagnosticul clinic, cât și confortul pacientului, dar mai multe studii clinice sunt necesare pentru validare și pentru a determina cum poate informația obținută de la aceste noi aparate să fie integrată într-un algoritm de tratament reușit, având ca scop rezultate chirurgicale și calitate a vieții maximale.

Abrevieri: MRI: rezonanță magnetică; PET: tomografie cu emisie de pozitroni; WHO: Organizația Mondiala a Sănătății; LGGs: Glioame slab diferențiate; FLAIR: rezonanță magnetică cu atenuare a fluidelor; DSC-MRI: RMN cu contrast dinamic de susceptibilitate; DCE-MRI: RMN cu contrast dinamic; Ktrans: coeficient de transfer de contrast; rCBV: volumul sanguin cerebral relativ; LOH: pierderea heterozigozității; DWI: imagistică de difuziune ponderată; ADC: coeficient de difuziune aparentă; FA: anizotropie fracționară; DTI: imagistică de tensiune a difuziunii; DKI: imagistica cu indice de aplatizare al difuziunii; MRS: spectroscopie de rezonanță magnetică; MRSI: spectroscopie de rezonanță magnetică; 1H-MRS: spectroscopie de rezonanță magnetică cu protoni; HGGs: glioame inalt diferențiate; 18F-FDG PET: PETcu 2-(18F)-fluoro-2-deoxi-D-glucoză (FDG); CT scan: computer tomograf; 11C- methionine PET (MET PET): PET cu L-(metil-11C)-metionină; 18F-FET PET: PET cu O-(2-18F-fluoroetil)-L-tirozină; 18F-FDOPA PET: PET cu 3,4-dihidroxi- 6-18F-fluoro-L-fenilalanină; 18F-FLT PET: PET cu 3-deoxi-3-18F-fluoro-timidină; 18F-FMISO PET: PET cu 18F-fluoromisonidazol.

Cuvinte cheie: glioame slab diferențiate, neuroimagistică, rezonanță magnetică, tomografie cu emisie de pozitroni, factori de prognostic, spectroscopie cu rezonanță magnetică, imagistică hibrid, ghidaj bioptic, răspunsul la tratament

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ABSTRACT

Background: Neuroimaging plays a key role in the diagnosis and management of low grade gliomas. An extensive and non-invasive assessment of location, tumor metabolism and proliferation rate, its invasiveness and interaction with neighboring tissue, as well as its response to therapy and early identifications of recurrences is very helpful for clinical management.

Methods: The authors evaluated scientific papers collected from the literature (Medline and the Cochrane Library to date) and have tried to determine what is the best neuroimagistic management algorithm in low grade gliomas and how it can improve the surgical strategy, global outcome and quality of life of patients.

Results and conclusions: The use of MR and PET protocols can assist considerably in confirming a diagnosis (though biopsy is never to be excluded), providing prognosis information even from the beginning, and making possible the correct individual therapeutic management protocols. These techniques also contribute to surgical planning, identification of most active tumor parts and the extent of tumor. Gathering both MRI and PET in one session on a hybrid machine is assumed to improve both clinical diagnosis and patient comfort but more clinical trials are still needed to validate and determine how the information, provided by these new machines is integrated into a successful treatment algorithm designed for maximum surgical results and quality of life.

Abbreviations: MRI: Magnetic resonance imaging; PET: Positron emission tomography; WHO: World Health Organization; LGGs: Low-grade gliomas; FLAIR: fluid-attenuated inversion recovery MR image; DSC-MRI: dynamic susceptibility contrast imaging; DCE-MRI: dynamic contrast-enhanced imaging; Ktrans: contrast transfer coefficient; rCBV: relative cerebral blood volume; LOH: loss of heterozygosity; DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient; FA: fractional anisotropy; DTI: Diffusion tensor imaging; DKI: Diffusion kurtosis imaging; MRS: Proton Magnetic Resonance Spectroscopy; MRSI: Magnetic resonance spectroscopic imaging; 1H-MRS: Proton magnetic resonance spectroscopy; HGGs: High-grade gliomas; 18F-FDG PET: 2-(18F)-fluoro-2-deoxy-D-glucose (FDG) PET; CT scan: computed tomography scan; 11C- methionine PET (MET PET): L-(methyl-11C)-methionine positron emission tomographyl; 18F-FET PET: O-(2-18F-fluoroethyl)-L-tyrosine positron emission tomography; 18F-FDOPA PET: 3,4-dihydroxy- 6-18F-fluoro-L-phenylalanine positron emission tomography; 18F-FLT PET: 3-deoxy-3-18F-fluorothymidine positron emission tomography; 18F-FMISO PET: 18F-fluoromisonidazole positron emission tomography.

Key words: low-grade glioma, neuroimaging, magnetic resonance imaging, positron emission tomography, prognostic factors, MR spectroscopy, hybrid imaging, biopsy guidance, response to therapy

INTRODUCTION

Diffuse infiltrative low-grade gliomas (LGG) of the cerebral hemispheres in adults are a group of tumors with distinct clinical, histological and molecular characteristics. The management of such tumors is still controversial. (1)

In LGG neuroimaging plays a crucial role. Starting of a “watch and wait” management plan has been frequently based solely on imaging. Conventional MRI is a valuable method in conducting a differential diagnosis, assisting surgery, planning radiotherapy and surveying treatment response, but it focuses on structural changes within tumours and often provides limited information only. (**Fig. 1**)

Conventional MRI is the major investigation of choice in the diagnosis of LGG. The appreciation of surgical results for radical resections in MRI is performed on postop MRI imaging. (**Fig. 2** and **3**)

Advances in MRI technology have allowed the development of new techniques (perfusion MRI, diffusion weighted (DWI) and diffusion tensor imaging (DTI), MR spectroscopy). These novel techniques together with PET scanning can investigate changes in cellularity, vascularity and metabolism and thus contributing to the differentiation of low-grade gliomas than higher grade tumors or other conditions. These procedures can also provide prognostic information, identify early transformation and allow better guiding for performing

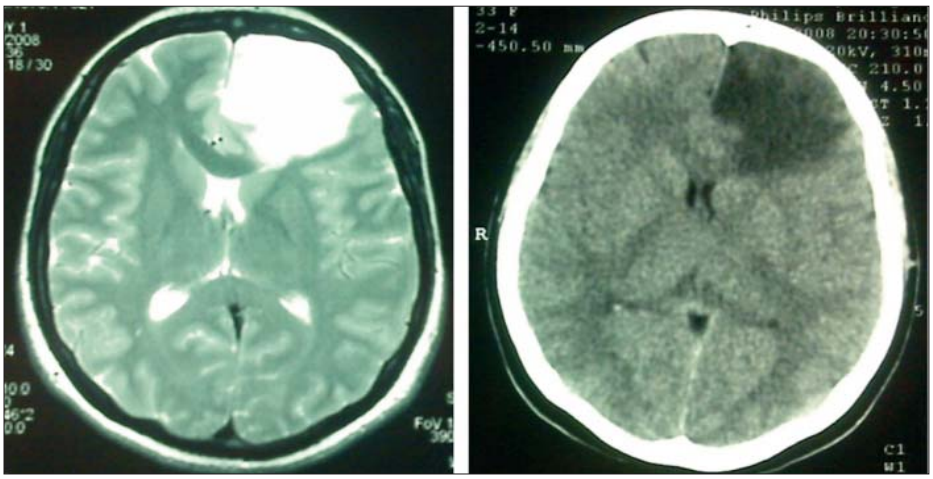

Figure 1. T1 and T2 MRI Aspect in a patient with left frontal low grade glioma

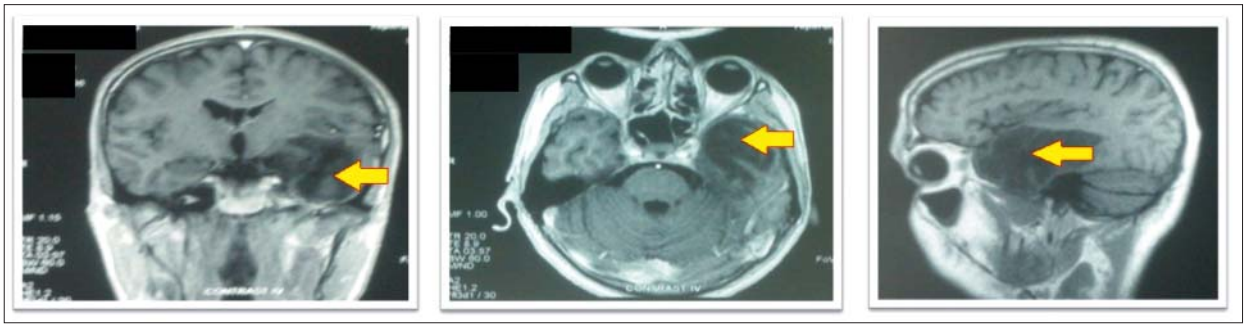

Figure 2. Conventional MRI in a patient with low grade glioma

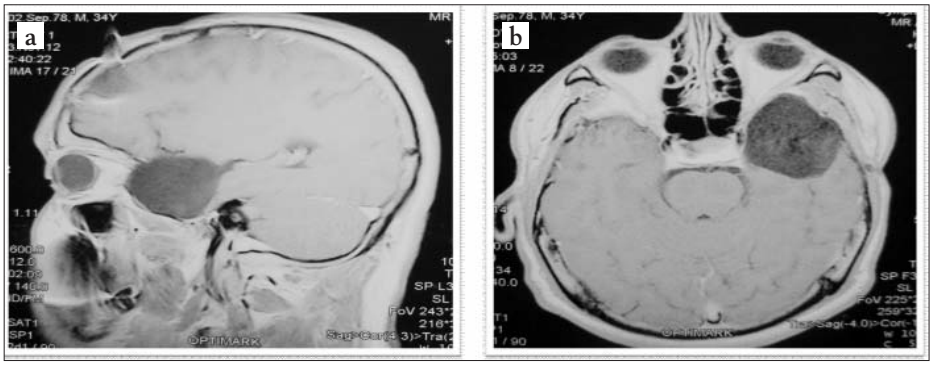

Figure 3. (a,b) MRI aspect in a patient with left temporal low grade glioma

biopsies or other therapies.

LGGs appear as low-signal mass lesions on T1-weighted MRI and high signal on T2-weighted and FLAIR sequences. Contrast enhancement is usually absent, but this feature cannot differentiate between high grade and low grade gliomas because of the fact that 16% of high grades do not enhance contrast (2); when present contrast enhancement may indicate a focal area of high-grade transformation. Although some tumors, particularly WHO Grade II oligodendrogliomas, have stable patch-like contrast enhancement in 50- 60% of all cases (3, 4) 38% of all anaplastic oligodendrogliomas do not enhance contrast (4).

The margins of low grade tumours are often poorly defined on T1-weighted imaging and better demonstrated on T2-weighted imaging. The use of

sequences such as fluid attenuated inversion recovery (FLAIR) shows the extent of these tumors very well while being particularly useful in regions around the ventricles.

Perfusion MRI

Dynamic susceptibility contrast MRI (DSC-MRI) allows measurement of relative cerebral blood volume (rCBV) that correlates with both tumor vascularization measured by classic angiography and histologic measurement of tumor neovascularization (5). Some studies have shown that the relative CBV of gliomas correlates with the glioma grade (6, 7). Increase in rCBV in LGGs predicts high-grade transformation before gadolinium enhancement occurs (8). It has been reported that oligodendrogliomas have significantly higher rCBV (7, 9). See **fig. 4**.

Dynamic contrast-enhanced imaging (DCE-MRI) assesses the permeability of the blood-brain barrier with the help of the transfer coefficient, Ktrans, which is related to tumor grade, but the correlation is weaker than that for rCBV (1, 6, 10).

Many studies have showed that low-grade gliomas have a significantly lower rCBV than glioblastomas (5, 11, 12, 13, 14, 15, 16). Difficulties arise in finding a threshold that can differentiate between high- and low-grade gliomas because of the use of different acquisition techniques and methods of reporting the rCBV. A lower ratio is computed when a spin echo technique is used, due to its sensitivity for the microvascular component, comparative with using a gradient echo technique that reflects CBV from all vessels (16, 17).

Studies using spin echo sequences have suggested that rCBV (cutoff ratio of 1.5) was a sensitive marker (75-100% range) for high-grade histopathology, however the procedure's low specificity (40-97% range) must be mentioned.

No tumor with nCBV (normalized CBV) region of interest less than 1.5 was high grade (100% predictive value for excluding high grade) (7).

As for gradient echo sequences varying thresholds were reported. A high specificity was computed when rCBV was in the range of 1.75-2.9, as a threshold of 3.5 led to increased sensitivity (15, 18). Grading gliomas using perfusion parameters in the case of an individual patient is difficult because of the marked overlap of rCBV values in different tumour grades especially for differentiating WHO Grade III from either WHO Grade II or WHO Grade IV gliomas (5,14, 15, 16, 17).

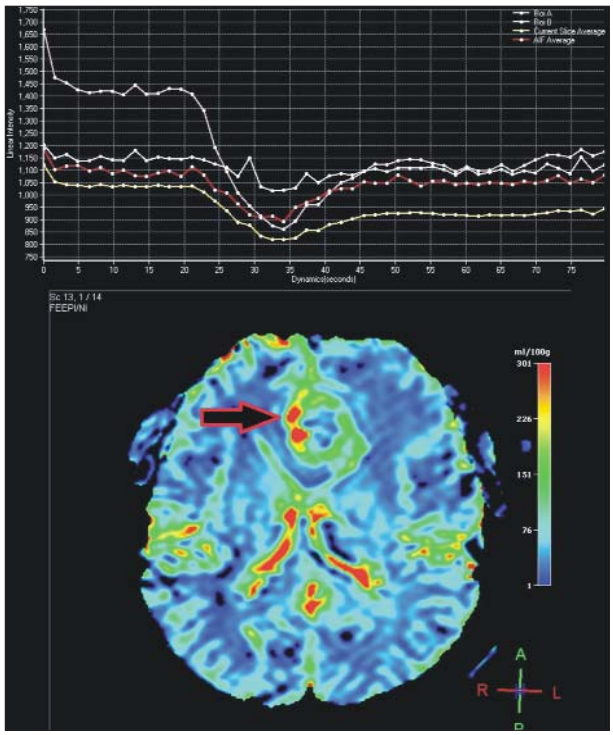

Figure 4. Example of Perfusion MRI
Adapted after J. Abrigo et al., CT perfusion in brain tumors : institutional experience in 12 patients and comparison with MR. perfusion. ECR 2012 / C-0264 DOI: 10.1594/ecr2012/C-0264

Due to the limitation of the hot-spot method some authors proposed histogram analysis of normalized CBVs from the entire tumor volume thus increasing diagnostic accuracy (19, 20). Compared with the hot-spot method, the histogram method has higher interobserver agreement, sensitivity, and negative predictive value and equal specificity.

For differentiation between low and high grade tumors, the rCBV cutoff tends to be bigger in oligodendrogliomas at a ratio of about 2.14 (100% specificity and 86% sensitivity) than the astrocytic one (21). The rCBV is in most cases slightly more elevated in tumors with 1p19q deletion (22, 23). In a population of patients with histologically proved gliomas, the histogram method may differentiate high-grade gliomas from low-grade gliomas and therefore identify oligodendroglial tumors without LOH on 1p/19q with high specificity and sensitivity (24).

An elevated rCBV indicates a poor prognosis with short progression-free survival time in patients with low-grade brain tumors. A rCBV threshold of 1.75 could differentiate between a prolonged survival group (median time to progression approximately 10 years) and a poor prognosis group (median time to

progression less than one year) (25, 26, 27). A recent follow-up study has shown that significant increases in rCBV can precede the transformation of LGG and new contrast enhancement by up to 12 months (8).

Low rCBV ratios could identify areas of radiation necrosis; rCBV values below 0.6 were reported as being predictive of radiation necrosis, as values bigger than 2.6 were predictive of tumor aggressivity. A Thallium chloride 201Tl single-photon emission tomography (201Tl-SPECT) may be useful for differentiation in cases having rCBV between 0.6 and 2.6 (28).

Percentage of signal intensity recovery (PSR) was proposed to be an even better variable helping to distinguish whether an enhancing lesion was the result of recurrent metastatic tumor or radiation necrosis. Values higher than 76.3% of PSR were indicative of radionecrosis with very high sensitivity and 100% specificity (29).

Stereotactic biopsies taken in regions with highest rCBV in non-enhancing tumours showing a heterogeneous perfusion can improve diagnosis accuracy. These biopsies demonstrated oligodendroglial differentiation or anaplastic differentiation whereas those taken in areas with uniformly low rCBV were WHO Grade II diffuse astrocytomas (30).

Diffusion-weighted and diffusion tensor MRI

Diffusion-weighted (DWI) imaging assesses the motion of water molecules within tissues. The appearance of low-grade gliomas on diffusion-weighted (DWI) imaging is variable. The high signal on DWI images is largely a result of a T2-weighted 'shine through' effect and is more dependent on the T2-weighted appearance (31).

Apparent diffusion coefficient (ADC, mm2/s) and fractional anisotropy (FA) are commonly accepted as measures of water diffusion. The ADC value correlates with both edema and blood-brain barrier (BBB) permeability (32). There is an inverse correlation between ADC and tumor cellularity (33, 34, 35).

Solid higher grade gliomas are correlated with low values of ADC (36, 37), while low-grade gliomas have a significantly increased ADC compared to high grade tumors (34, 35). ADC is significantly lower in oligodendrogliomas rather than low-grade astrocytomas (38). Within oligodendrogliomas the tumors with 1p19q deletion have lower ADC values (39). In a recent study, the authors showed that the combination of minimum ADCs and ADC difference values facilitated the accurate grading of astrocytic tumors (40).

Using DWI to differentiate radiation necrosis from tumor recurrence following therapy has seemed to be of little value for the individual patient due to the overlap of ADC values for necrosis and recurrence as wlll (41), although, in eighteen patients with histologically proved high grade glioma who underwent radiation therapy the utilization of ADC ratios of enhancing tissue were reported being valuable in this differentiation with no overlapping data between the groups (42, 43). ADC histogram analysis could bring supplementary information and assist in identifying of a mixture of necrosis and recurrence (44).

Diffusion tensor imaging (DTI) (see **fig. 5**) is a modification of DWI that is sensitive to the directional diffusion of water (anisotropy). Fractional anisotropy (FA) derived form DTI provides the best quantitative information regarding directional diffu-

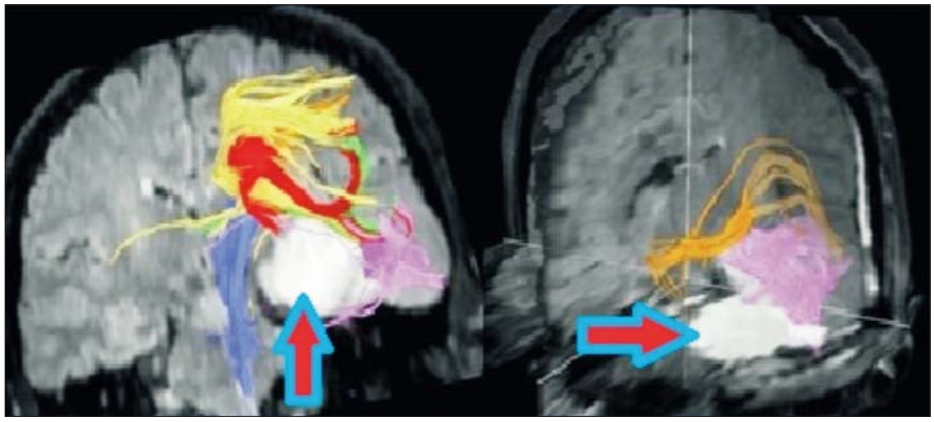

Figure 5. Diffusion tensor imaging in a left, temporal, low grade glioma

sivity of water molecules in tissues.

The FA threshold between low-grade and high-grade gliomas was 0.188 (45). A high FA value was suggested to be highly correlated with cell density. In contrast to tumor tissues, high FA values were observed in normal brain tissue due to strong directionality of water diffusion (46). FA values derived from DTI reflect interstitial characteristics of perilesional tissues of brain tumors. Tumor infiltration of perilesional tissues is reflected by low FA while high FA shows better tissue integrity (1004). Diffusion kurtosis imaging (DKI) is a relatively recently developed method suitable for the detection of microstructural changes. Its principal metric, mean kurtosis (MK), is thought to be an index of microstructural complexity. The mean kurtosis had 71% sensitivity and 82% specificity at an optimal threshold of 0.52 for differentiating high-grade from low-grade gliomas in 28 patients with brain glioma (48).

Magnetic resonance spectroscopy

Proton Magnetic Resonance Spectroscopy (MRS) (see **fig. 6, 7** and **8**) allows the non-invasive study of metabolism from either a single, small region of interest (single voxel spectroscopy) or multiple regions (multivoxel or chemical shift imaging; MRSI). Several metabolites in cerebral tissue, such as N-acetylaspartate (NAA – marker of neuronal viability; resonates at 2.0 ppm), choline compounds (Cho - marker of cellular membrane turnover; resonates at 3.2 ppm), creatine and phosphocreatine (Cr - a marker of energy metabolism; resonates at 3.0 ppm), lactate (marker of anaerobic metabolism; resonates at 1.3 ppm) and lipid (marker of severe tissue damage with liberation of membrane lipids; resonates at 1.3 ppm), can be measured by means of proton MRS (1H-MRS). Many studies have shown that 1H-MRS is helpful for differentiating proliferative tumors from normal tissue (49-51).

All gliomas show a spectrum with an increased choline and reduced NAA. Peaks of lipid and lactate are elevated in higher grade gliomas, but they are also elevated (rarely) 3 in low-grade gliomas (52, 53, 54, 55), so that the typical spectrum for LGG shows elevated choline and decreased N-acetylaspartate, but similar abnormal spectra may be seen in non-neoplastic lesions.

For differentiation between low and high-grade gliomas a 2.02 cutoff value for maximum Cho was reported (56). In addition to high-grade tumors elevated choline levels were reported for pilocytic astrocytomas (57) and low-grade oligodendrogliomas. For oligodendrogliomas, a cutoff of 2 for normalized choline was indicated by for the separation between low- and high-grade oligodendrogliomas (58).

Creatine (Cr) is decreased in brain tumours, but the reduction is, however, small and does not appear to be related to the grade of tumour (52). Averaged normalized creatine values higher than 0.93 seem to indicate a shorter time to progression in WHO grade II and III astrocytomas (59). In a recent study, the normalized Cr in low grade gliomas was a significant predictor for tumor progression and for malignant transformation, decreased Cr (relative Cr < 1.0) being beneficial (60).

Increased levels of myo-inositol (mI - resonates at 3.5 ppm) have been reported to be higher in grade II gliomas than in patients with anaplastic astrocytomas (61, 62), but also in patients with gliomatosis cerebri even though choline/creatine is normal(63).

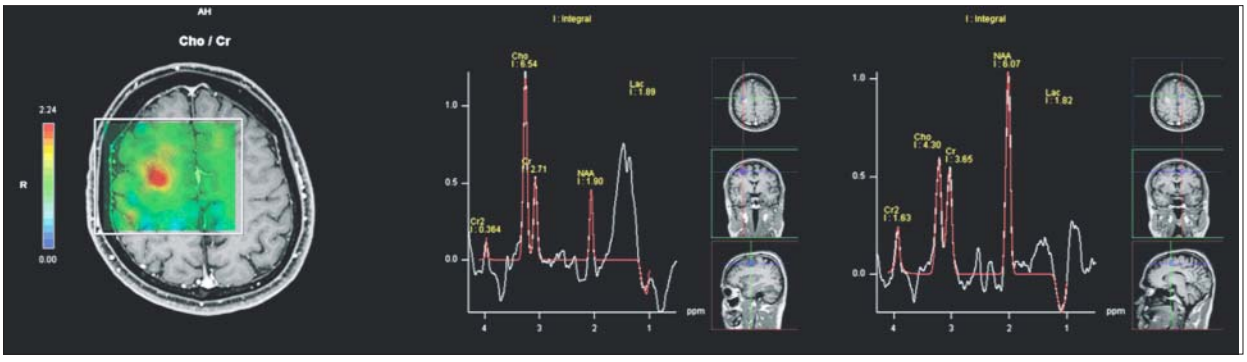

Figure 6,7,8. Magnetic resonance spectroscopy in apatient with low grade glioma
Courtesy of Prof. Horia Ples MD., PhD

A review of the literature demonstrates maximal values obtained for Cho/Cr and Cho/NAA ratios and minimum values for NAA/Cr to be of utility in differentiating between LGGs and HGGs (52, 61, 64, 65). In a recent study the ratio of NAA/Cho was the best discriminator ($p<0.001$) in differentiation between low and high grade glioma (66). It can be shown that low-grade gliomas have a significantly lower Choline/Cr ratio (18, 53, 54, 55, 67), and an increase in NAA (18, 53, 68, 54, 55, 67) comparative with HGGs. It is therefore possible to differentiate between high-and low-grade gliomas with sensitivity of 73-92% and specificity of 63-100%, but combining MRSI and DSC MRI for guiding the spectral measurement location in regions with elevated flow, the sensitivity is significantly improved (18, 69, 70, 71, 72, 73).

MRS has a role in differentiating low-grade gliomas from other conditions, like focal cortical developmental malformations or demyelinating disease, which can present with similar clinical symptoms and appearances on conventional imaging. MRS should perhaps be seen as an adjunct technique that may contribute to differential diagnoses that are being considered on the basis of MRI, clinical and other information.

Attempts to monitor low-grade glioma transformation using MRS had a specificity of only 57.1% (74) and showed no convincing evidence that 1H-MRSI can appropriately observe and follow-up of patients with suspected LGG (75).

Using MRS to assess response to therapy in LGG illustrated in a group of 12 patients with LGG treated with temozolomide the decrease of the choline peak correlated with a reduction in tumour volume and an important increase in NAA but only in three patients, and these metabolic changes did not apparently precede changes in tumour volume (76).

In a recent study assessing progression of gliomas after resection and radiochemotherapy by 1H-MRS (Cho/Cr ratios) and 18F-FDG PET that included twelve patients (six grade II and six grade III), MRS was more accurate in low-grade gliomas (80% in low-grade tumors), and 18F-FDG PET was more accurate in high-grade gliomas (100% in high-grade gliomas)(78).

Differentiation of radiation necrosis from tumour recurrence is one of the most important applications of MRS in a clinical setting. Regions of radiation necrosis exhibit lower NAA/Cho and NAA/Cr ratios and higher Cho/Cr ratios than tumour progression (79, 80). The presence of lactate can be noticed with either pathology and suggests that ischaemia is the underlying mechanism of radiation injury (79). Although MRS can identify pure tumor and pure radiation necrosis, it is not able to differentiate the mixed picture alone, which is probably the most common setting (80, 81).

Positron emission tomography (PET) imaging

PET (see **fig. 9**) can obtain useful information on tumor hypoxia, necrosis, proliferative activity, or vasculature using three groups of PET tracers that investigate glycolytic metabolism, protein synthesis and nucleotide uptake as markers of tumor proliferation. Some new radiotracers for studying membrane turnover have been developed but their

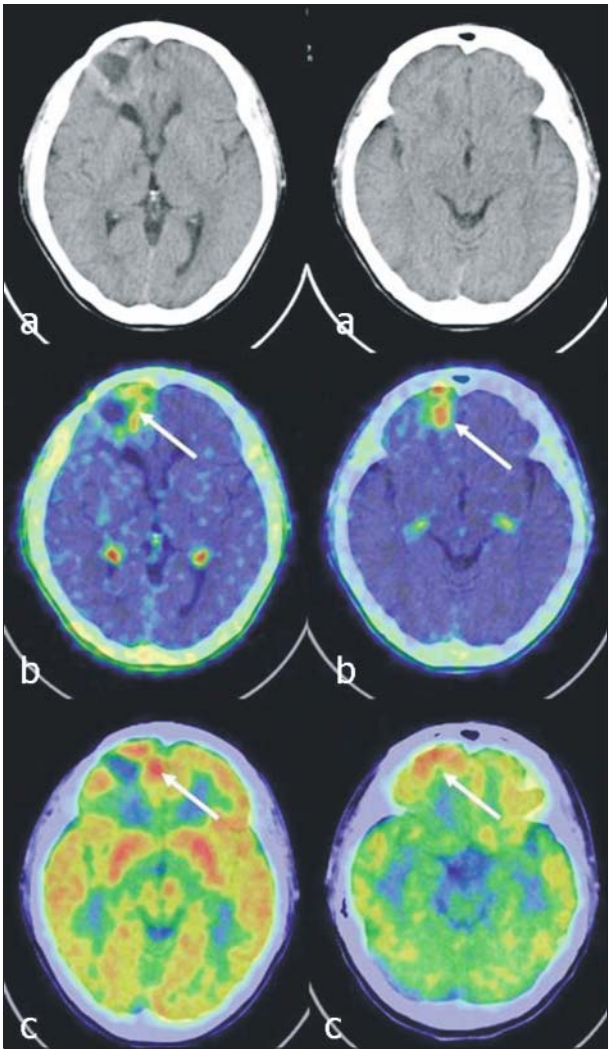

Figure 9. PET imaging in frontal lobe tumor.
Adapted from T. Win et al., Fluorine-18 fluorocholine (FCH) PET/CT in differentiating radionecrosis from viable gliomas: a pictorial essay

use has yet to be deter¬mined.

Imaging glycolytic metabolism: 2-(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) PET ^{18}F-FDG is the tracer used for quantification of the metabolic rate of glucose. Intracellularly it is phosphorylated to ^{18}F-FDG-phosphate that accumulates locally. The fluorinated glucose analogue 2-(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) has high sensitivity (although poor specificity) for identifying areas of increased tumor metabolism. The hyperglycolysis seen in tumors is due to increases in glucose transport across the blood brain-barrier and cell membranes and increases in the principal enzymes of glucose metabolism.

Low-grade gliomas tend to have the same or lower uptake rates when compared to normal grey and white matter, whereas high-grade gliomas tend to exhibit increased uptake of FDG (82, 83). Cutoff levels of ratios of 18F-FDG uptake in tumors to that in white matter > 1.5 and tumor to gray matter > 0.6 were useful to distinguish low grade (grades I and II) from high grade gliomas (grades III and IV) with a sensitivity of 94% and specificity of 77% in 58 consecutive patients (84). Delayed imaging (3–8 h after injection) leads to improved differentiation (85).

Areas of increased FDG uptake correlate in low-grade gliomas with tumor anaplasia (86, 87). The transformation of low-grade gliomas to a higher grade might be possible to detect with FDG PET before anatomical changes appear on CT scan (88). FDG PET could identify targets for stereotactic biopsies far better than contrast enhanced CT (89).

The FGD uptake has been suggested to be lower in low grade astrocytomas than in oligodendrogliomas (82) and significantly lower in WHO Grade II oligodendrogliomas than anaplastic oligodendrogliomas (90). Oligodendrogliomas with intact chromosomes 1p19q have lower FDG uptake comparatively with that measured in low grade oligodendrogliomas with loss of 1p19q heterogeneity (91).

A newly detected hypermetabolism, weeks after resection or treatment, indicates a recurrent tumor or progression from low-grade to high-grade glioma. The sensitivity was improved by MRI co-registration. FDG PET was reported having 80%–90% sensitivity and 50%–90%. specificity in differentiating radiation necrosis from recurrent high-grade gliomas (92). In 15 patients with low grade glioma, FDG PET distinguished recurrent brain tumor from radiation necrosis with 100% sensitivity and 75% specificity, recurrent tumours having increased metabolic activity whereas areas of radiation necrosis being hypometabolic (93).

The limitations to using FDG to assess brain tumours is that the uptake is non-specific and can occur in any region with an increase in metabolic activity and the uptake can vary greatly.

Imaging protein synthesis: amino acid PET studies.

Amino acid imaging has developed starting with the observation that malignant transformation leads to the increasing of amino acid transportation (94, 95), tumorous cells being able to up-regulate amino-acid transporters, and this process does not depend on a breakdown of the BBB (96). The low uptake in normal cerebral tissue and high uptake in tumor tissue of the aminoacid and aminoacid analogue PET tracers are particularly worthy for imaging brain tumors offering an advantageous normal/tumor contrast.

Most amino acid labelling studies have used ^{11}C since it does not change the chemistry of the molecule.^{11}C-methionine (L-(methyl-^{11}C)-methionine) or ^{11}C-tyrosine (L-1-(^{11}C)-tyrosine) are the most commonly used amino acids. Because of the too short half-life of ^{11}C (20.4 min), which means production has to be made when it is required, ^{18}F-labeled aromatic amino acid analogues (half life of 109 min) have been developed for tumor imaging. O-(2-18F-fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy- 6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA) have showed similar tumor uptake with 11C-methionine (97,98).

In gliomas, 11C- methionine uptake is greater in high-grade than in low-grade tumors (99, 100, 101) and is increased in most low-grade gliomas in the absence of BBB damage (102). This investigation provides additional information when used in combination with 18F-FDG PET for diagnosis of brain tumours. In 45 patients with brain lesions (including 10 benign lesions), all of them being isometabolic or hypometabolic to glucose, 89% of brain tumour showed increased methionine uptake (the mean uptake ratios tumour/brain was 2.54 +/- 1.25) comparatively with FDG PET ratios where the mean was 0.92 +/- 0.34. The methionine uptake was normal or decreased in all benign lesions (103).

Using methionine PET for glioma grading showed in 102 patients with histologically confirmed glioma a statistical significant difference ($P < 0.001$) of T/N ratios (the ratio uses the mean standardized

uptake value in tumor and contralateral normal cortex) values in high grade glioma (2.15 ± 0.77) than in low grade glioma (1.56 ± 0.74) (104). Other studies reported similar findings, but the difference between grade 1 and 2 or 3 and 4 was not always statistically significant (105, 106) and methionine PET appears to be a more sensitive marker than FDG (90, 107).

With regard to tumors extent and infiltration into surrounding tissue, the assessment of ^{11}C-methionine uptake is superior to FDG PET (102, 108, 109, 110, 111, 112), conventional contrast-enhanced MRI (113) or MRS, detecting solid tumors and the infiltration zone with high sensitivity and specificity (114).

For the discrimination of brain tumors from non tumoral lesions, a sensitivity of 76% (79% for low grade glioma) and a specificity of 87% (115) have been described. In a group of 39 patients aged from 2 to 21 years, ^{11}C- methionine PET was very helpful (sensitivity 83% and specificity 92%) in distinguishing brain neoplasm by non-tumorous brain lesions when data provided by routine diagnostic procedures (CT and MRI) were not enough to obtain a sure diagnostic. A threshold of 1.48 of relative methionine uptake made possible a correct identification of 8 from out 9 non tumorous lesions (116).

^{18}F-FET PET has not been shown useful in differentiating low- from high-grade tumors, although some investigators reported that the kinetic profile in ^{18}F-FET uptake for low- and high-grade tumors might be a useful feature for distinguishing the 2 types of tumors (117). High-grade tumors are characterized by an early peak in tracer uptake, which is followed by a decline whereas low grade tumors exhibit a steadily and slightly increasing contrast with time (118, 119, 120).

Some studies reported a significant clinical role of amino acid uptake in prognostication and survival for patients with low-grade glioma. The tumor/normal brain methionine uptake ratio > 2.2 was statistically associated with poor outcome for 28 patients with WHO Grade II glioma (121), and was obviously identified as an independent prognostic factor in 46 patients aged > 40 years (122). Increase methionine uptake was reported being indicative of malignant transformation in LGG. These results were also true for oligodendorgliomas. Mean increase of methionine uptake was 54.4% in patients with progression versus 3.9% when the disease was stationary in twenty-four patients with histologically proven glioma (123) whereas unchanging or decreasing methionine uptake in tumor area after radiotherapy appears to be a favorable sign (124).

Baseline ^{18}F-FET uptake and a diffuse versus circumscribed tumor pattern on MRI were reported as highly significant predictors ($P<0.01$) of prognosis in 33 consecutive patients with histologically confirmed LGG. The poorest outcome was registered in patients with diffuse pattern on MRI and FET uptake on PET (progression in 100%, malignant transformation in 78%, and death in 56%). The patients having a circumscribed pattern and no FET uptake showed only 18% progression, no malignant transformation and no death (125). Early differentiation between recurrent tumor and radiation necrosis is of notable interest in monitoring treatment effects. The high sensitivity of ^{11}C- methionine PET coregistered to MRI and its sensitivity around 75% makes this technique better than FDG PET in fulfilling of this purpose (111, 126, 127, 128).

The diagnostic value of ^{18}F-FET PET in patients with clinically suspected recurrent glioma (117) showed that ^{18}F-FET was able to distinguish between recurrent tumour and therapy-induced benign changes with 100% accuracy. In this study, focal and high ^{18}F-FET uptake was considered suggestive of tumour recurrence, whereas low and homogeneous uptake around the resection cavity was considered a benign post-treatment change.

In another study, among patients suspected of having recurrent tumor as revealed by MRI 92.9% specificity and 100% sensitivity were computed for ^{18}F-FET comparative with 93.5% sensitivity and 50% specificity for MRI ($P < 0.05$) (129). Thus, the ^{18}F-FET PET emerges as a worthy tool in diagnostic of recurrent tumor. A higher diagnostic accuracy was reported for the combined analysis of ^{18}F-FET PET parameters (tumor/brain ratios, "time-to-peak" (TTP), time-activity curve pattern) than modifications of contrast enhancement on MR imaging (accuracy, 81% vs. 63%; $P = 0.003$) in 27 patients with LGG (130).

Some studies investigated the role of amino acid PET in low-grade glioma for monitoring the tumor response to radio- and chemotherapy. A decrease in Met uptake was reported in 7 patients with oligodendroglioma (WHO grade II) treated with PCV, a finding statistically more significant than the decreasing of tumor volume measured on FLAIR MR images (131).

A similar response was recorded in 11 patients

with LGG that underwent temozolomide

chemotherapy and that were progressively monitoring by FET PET. The metabolic active tumor volume started to decrease with 3 month earlier than the volume measured on MR imaging (132). The high sensitivity in early detection of treatment response and the ability to identify non-responders make the amino acid PET a valuable tool in monitoring patients with LGG.

There have been only few studies, which included a small number of patients, which analyzed the usefulness of amino acid PET in monitoring response to radiotherapy in LGG patients and the results are somewhat contradictory. Roelcke et al. found no difference in MET and FDG PET uptake, in 30 surgically treated patients with low grade astrocytoma who did (13 patients) or did not (17 patients) undergo fractionated external radiotherapy during a period of 94 month postoperatively (88). In another study, a significant decrease of MET uptake was recorded one year after 125I seed implantation in 10 patients with LGG, although FDG PET uptake did not change (133).

A number of studies investigated the ability of MET or FET PET in improving the diagnostic yield of stereotactic biopsy (109). MET was a better choice than FDG PET in 45 PET guided stereotactic brain biopsies, all tumor exhibiting an abnormal MET uptake, but only 33 had an abnormal FDG uptake (134). Similar to MET PET, FET PET identified a metabolic hot spot in 76% while FDG PET only in 28% cases in a series of 52 patients (24 LGG, 19 HGG, 9 others) (135). 11C-methionine PET therefore has special value in low-grade gliomas: for differentiation from nontumourous lesions, for detection of recurrences, for indicating changes in grade of progressing disease, and for potentially allowing a better prediction of prognosis.

Evaluation of ^{18}F-FDOPA PET imaging, in 81 patients with brain tumors, showed that either tumour grade or their ability of contrast enhancing did not significantly affect tracer uptake (136) a behaviour found in most studies using other amino acid tracers. ^{18}F-FDOPA PET demonstrated excellent visualization in 15 patients with low-grade glioma being positive in all recurrent or newly diagnosed glioma and negative in patients in remission. It was superior to both ^{18}FLT PET (positive in 4 of 13 cases) and ^{18}FDG PET (in 7 of 13 cases) and was more sensitive and specific than ^{18}F-FDG for evaluating recurrent tumors (137).

Some studies suggested that ^{18}F-FDOPA PET might be valuable for distinguishing recurrent tumor from radiation necrosis with a sensitivity and specificity (81.3% respectively 72.5%) (138) similar with C-MET (79% respectively 75%) (128) and F-FET PET (74% and improved specificity (90%) (130), although a larger series of cases is needed for confirmation.

Imaging DNA synthesis with labelled pyrimidine analogues

Labeled nucleosides are indicators of cellular proliferation. Thymidine has long been used for labelling in PET studies because it is only incorporated into DNA and not RNA.

Uptake of thymidine correlates with thymidine kinase-1 activity, an enzyme expressed during the DNA synthesis phase of the cell cycle, which is increased in proliferating cells and low in resting cells. The thymidine analog 3-deoxy-3-^{18}F-fluorothymidine (^{18}F-FLT) was developed as a non-invasive tracer of tumor cell proliferation (139, 140). FLT uptake involves a combination of mechanisms which include increased transport and phosphorylation (141). Phosphorylation of ^{18}F-FLT intracellularly by thymidine kinase-1 results in getting caught of the negatively charged ^{18}F-FLT monophosphate (142).

FLT uptake is considerably elevated in high-grade gliomas (141, 143, 144, 145, 146). Low grade gliomas frequently show no substantial FLT uptake (141,145). This tracer showing low uptake in normal brain provides a good delineation of grade III and IV tumors with a high tumor-to-normal ratio (141,146). A significant correlation of ^{18}F-FLT uptake was seen with Ki-67 expression in newly diagnosed glioma; the correlation was weaker in recurrent glioma (141, 143, 144, 147, 148, 149). Increased FLT uptake appears to be a good predictor of tumour progression and overall survival either in LGG or HGG (143, 150).

In a recent study ^{18}F-FLT PET appeared to be better than ^{11}C-methionine PET in tumor grading and assessment of proliferation in 41 patients with different gliomas, and the combination with ^{11}C-methionine PET added no significant information (151). Compared to FDG PET, FLT is more a sensitive in detecting tumour due to the improved contrast-to-background ratio (143, 144).

The absolute 18F-FLT uptake and sensitivity for tumoral detection were significantly lower than that of ^{11}C-MET PET in 23 patients with gliomas of

different grades (eight patients with WHO grade II), but the uptake ratios for tumor to normal brain were higher for ^{18}F-FLT PET. The accurate extent of tumor was better characterized by co-registration of these various imaging modalities (^{18}F-FLT and ^{11}C-MET PET, and gadolinium-enhanced MRI).(141)

Using ^{18}F-FLT PET for monitoring treatment effects in patients with recurrent malignant gliomas made a distinction between responders and non-responders to a combination therapy (bevacizumab and irinotecan): ^{18}F-FLT PET at 2 and 6 week predicted survival better than did MRI (152). Thus, ^{18}F-FLT has the potential to monitor treatment response and to serve as a prognostic marker.

Imaging hypoxia

Hypoxia is associated with tumour progression and resistance to radiotherapy (153). ^{18}F-Fluoromisonidazole (^{18}F-FMISO) is a nitroimidazole derivative that has been developed as a PET agent to image hypoxia (154). Metabolites of ^{18}F-fluoromisonidazole are trapped exclusively in hypoxic cells (155).

PET studies have shown that it accumulates in high grade tumours but not in low grade gliomas (156, 157, 158). The volume of hypoxia in a glioma as determined by ^{18}F-FMISO uptake before initiation of treatment was related to aggressiveness as assessed by serial MRI (159) and to progression and survival after radiotherapy (160). More studies are still needed in low-grade gliomas.

Imaging membrane turnover

Choline and acetate have been used in PET studies for imaging membrane turnover.

The choline fluorinate version has a higher tumour-to-normal ratio (161) than the carbon type. In low-grade gliomas the uptake is comparable to normal brain. Anaplastic areas within a glioma show increased uptake and, as a result, may guide biopsies (161). The diagnostic accuracy of ^{11}C-choline PET is superior compared to ^{18}F-FDG PET, but is inferior to ^{11}C-MET PET (162, 163). 11C-choline PET seems to be superior to MRI and ^{18}F-FDG PET in discriminating tumour recurrence from radionecrosis (164) and in optimization of postoperative radiotherapy in patients with brain gliomas (165).

Small scale studies have showed significant difference in acetate uptake between low and high grade glioma. The ^{11}C-acetate uptake was higher even in tumours with little FDG uptake (166, 167), but there is only little uptake in low grade glioma. The ^{11}C-acetate seems to be a promising tracer for detecting and grading brain gliomas, but more studies are needed for quantification of its value.

CONCLUSIONS

The use of these new MR and PET techniques can assist the neuroradiologist, neuropathologist or neurosurgeon considerably in confirming a diagnosis, providing prognostic information, probably even from the beginning, and making possible the optimization of the individual therapeutic management.

These techniques also help in correctly describing the location of the tumor, identification of the most active regions and the extent of tumor, making accurate planning possible and radical resection possible.

The availability of the new MRI techniques is increasing these days; all modern MRI devices are able to perform perfusion and diffusion MR, as well proton spectroscopy.

The availability of PET imaging is more limited, but the developing of 18F-labeled aromatic amino acid analogues that need less logistic prerequisites for PET imaging has increased accessibility to FET-PET studies.

In recent years the recommendations to use amino acid analogues for brain tumor imaging have been included in the guidelines of the European and the German Association of Nuclear Medicine (168, 169).

The recent advances in the field of hybrid PET/MRI machines seem to gain increasing importance in the complex management of these particular lesions. The advantages of a single imaging session with lower examination exposure and integration of PET and MRI parameters are challenged by the duration of the exam. (170, 171, 172).

More clinical trials are still needed to validate and determine how the information, provided by these new MR and PET techniques could be integrated into a successful algorithm to optimize the individual therapeutic strategy for maximum surgical results and a better quality of life.

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