Comparison of diffusion tensor, dynamic susceptibility contrast MRI and $^{99m}$Tc-Tetrofosmin brain SPECT for the assessment of glioma proliferation

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Aims and objectives

Assessment of the grade and type of glioma is of paramount importance for prognosis. Tumour proliferative potentials may provide additional information on the behaviour of the tumour, its response to treatment and prognosis. The purpose of this study was to investigate the correlation between diffusion tensor imaging (DTI), dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) and $^{99m}$Tc-Tetrofosmin brain single-photon emission computed tomography (SPECT), and the tumour grade and Ki-67 labelling index in newly diagnosed gliomas.
Methods and materials

Fig. 1: A 45 year-old male patient with a glioblastoma. A. Contrast-enhanced T1-weighted magnetic resonance (MR) image. B. Relative cerebral blood volume (rCBV) map, the rCBV value was 5.9. C. Apparent diffusion coefficient (ADC) ratio was 1.75. D. The co-registered fractional anisotropy (FA) maps from diffusion tensor imaging (DTI). The FA value was 0.15.

References: radiology, University - Ioannina/GR
Patients: Successive patients with suspected glioma on brain MRI between December 2010 and January 2012 were included in the study. The institutional review board for clinical investigation approved the study protocol, and informed consent was obtained from all patients studied. Their lesions were investigated using DTI, DSC MRI and $^{99m}$Tc-Tetrofosmin brain SPECT. Histopathological diagnosis and grading of brain tumours was conducted according to the WHO 2007 classification for central nervous system (CNS) tumours [10]. The proliferative activity of each tumour was measured by deriving the Ki-67 proliferation index from immunohistochemical staining of tumor specimens.

MRI protocol: All MR examinations were performed on the same 1.5-tesla MR unit using a head coil. The imaging protocol consisted of:(a) a T1-weighted high resolution (1mmx1mmx1mm) 3-dimentional spoiled gradient echo sequence (TR:25 ms, TE:4.6ms, acquisition matrix:256x228, FOV:220mm), which was used for structural imaging before and after intravenous (iv) injection of gadolinium-DTPA; (b) a single shot, multi-slice, spin-echo planar sequence (TR:9807 ms, TE:131 ms, FOV:230 mm, acquisition matrix:128x128, slice thickness:3mm, max b-value:700 sec/mm², 16 non-collineardiffusion directions), which was used for measurement of the apparent diffusion coefficient (ADC) and fractional anisotropy (FA); (c) T2* gradient-echo, multishot (EPI) sequence (TR: 702ms, TE 30ms, flip angle: 40°, FOV: 250mm, slice thickness: 7 mm, gap: 0, EPI factor: 17, acquisition matrix: 128 × 51, dynamic scans: 50, imaging time per dynamic scan: 2.1 sec, 0.1 mmol/Kg gadolinium is typically injected via an 18 gauge iv catheter at 5 cc/sec, which was used for relative cerebral blood volume(rCBV) measurements; (d) T2-weighted turbo spin echo, axial plane, TR: 3000ms, TE: 90ms, acquisition matrix: 250×250, FOV: 230mm , slice thickness 6mm, gap 0.6mm;(e) T2-weighted inversion recovery based sequence for cerebrospinal fluid (CSF) suppression, sagittal plane,TR: 6300ms, TE: 120ms, slice thickness 6mm, gap 0.6mm, acquisition matrix: 250×250.

A semiquantitative method of image analysis was applied, by calculating the lesion-to-normal (L/N) ratio: a region-of-interest (ROI) was manually defined in the enhancing region of the lesion on a transverse slice showing maximal tumour size in T1-weighted imaging with contrast medium, and a second region was drawn on the contralateral normal brain side. Areas of necrosis were excluded. The L/N ratio was calculated by dividing the mean of values derived for every pixel in the given ROI in the tumour region with the mean values of the ROI in the normal region. The ROIs were evaluated for eligibility independently by two experienced neuroradiologists blinded to the final diagnosis and SPECT findings and possible disagreements were solved by consensus. (Fig.1)

$^{99m}$Tc-Tetrofosmin SPECT and image analysis: Brain SPECT was obtained 20-30 min after iv injection of 925 MBq (25 mCi) tracer activity. The radiopharmaceutical was prepared using a domestically available powder kit (Myoview™, General Electric Healthcare Ltd., Buckinghamshire, UK) that was reconstituted with technetium-99m
pertechnetate ($^{99m}$TcO$_4$) sterile solution in the Department of Nuclear Medicine. All studies were implemented in a dual-head #-camera (Millennium™ VG3, General Electric Medical Systems - Europe, Buc Cedex, France), equipped with a pair of high-resolution, parallel-hole collimators. The matrix was set at 128×128 pixels; the photopeak was centred at 140 KeV, with a symmetrical 10% window. The tomographic imaging parameters consisted of a 360°-rotation angle, a 3°-step-and-shoot technique, and an acquisition time of 30 sec per frame. Raw imaging data were reconstructed using the Butterworth-filtered back-projection algorithm, generating tomographic views of the brain in the 3 planes (transverse, coronal, and sagittal). Radiotracer accumulation in space occupying lesions was first assessed visually. A semiquantitative method of image analysis was then applied, by calculating the L/N uptake ratio: on the transverse SPECT slice with the highest tumoural tracer uptake, an ROI was manually defined around the lesion - in close reference to the MRI study - taking care to encircle those tumour areas with the highest tracer concentration. An identical second region was drawn over the contralateral side of normal brain. The ROIs were evaluated for eligibility by two independent experienced nuclear medicine physicians, who where blinded to the final diagnosis and MRI findings. The L/N ratio was calculated by dividing the average counts in the lesion ROI by the average counts in the contralateral normal region ROI.

**Histopathology and Ki-67 immunohistochemical assay:** An immunohistochemical method (avidin - biotin - peroxidase complex) was used on 4-µm thick, paraffin-embedded tumour sections for the demonstration of Ki-67 protein expression; the monoclonal murine antibody MIB-1 (Dako S.A., Glostrup, Denmark) was applied at a dilution of 1:20. The tumour sections were reviewed by two experienced neuropathologists and a quantitative estimation based on the percentage of positive cells was performed in the highest density of stained areas: all cells with nuclear staining of any intensity were considered positive; the Ki-67 index was defined as the percentage of positive cells in the total cells counted. Any discrepancy between the two neuropathologists was solved by consensus.
Results

During the study period a diagnosis of glioma was made in 25 patients (17 men, 8 women, aged 19-79 years; median 55 years). There were 18 cases of glioblastoma (GBM), 2 anaplastic astrocytomas, 1 gliosarcoma, 2 diffuse astrocytomas, 1 oligoastrocytoma and 1 oligodendroglioma. The Ki-67 index ranged from 1% to 80% (mean 19.4%).

Glioma Grade

Using the previously reported cut-off L/N value of 2.8 in $^{99m}$Tc-Tetrofosmin uptake [11], it was possible to differentiate low-grade from high-grade gliomas with 100% sensitivity and specificity. Low-grade gliomas had a significantly higher ADC ratio than high grade gliomas ($p=0.0009$). Using ROC curve analysis it was found that an ADC ratio of 1.43 could differentiate low-grade from high-grade gliomas with 100% sensitivity and 94.4% specificity. Low-grade gliomas had a significantly lower FA ratio than high grade gliomas ($p=0.01$). A FA ratio of 0.33 could differentiate low-grade from high-grade gliomas with 100% sensitivity and 66.7% specificity. When the oligodendroglioma was excluded from perfusion analysis because of inherent increased perfusion that these tumours exhibit, low-grade gliomas had a significantly lower rCBV ratio than high grade gliomas ($p=0.006$). A rCBV ratio of 1.63 could differentiate low-grade from high-grade gliomas with 100% sensitivity and 94.4% specificity (Fig.1,2).

Glioma Proliferation

When the relationship between $^{99m}$Tc-Tetrofosmin tumour uptake and proliferative activity was evaluated, as measured by the Ki-67 index, the radiotracer uptake by gliomas was found to be significantly correlated with cellular proliferation ($\rho=0.924$, $p<0.0001$). Regarding diffusion imaging significant negative correlation was demonstrated between the ADC ratio and the Ki-67 index ($\rho=-0.545$, $p=0.0087$). Significant correlation was also observed between the FA ratio and the Ki-67 index ($\rho=0.489$, $p=0.02$), and strong correlation between rCBV and the Ki-67 index ($\rho=0.853$, $p<0.0001$). Significant positive correlation was demonstrated between $^{99m}$Tc-Tetrofosmin L/N uptake ratio and rCBV ($\rho=0.808$, $p<0.0001$), and negative correlation between $^{99m}$Tc-Tetrofosmin L/N ratio and ADC ratio ($\rho=-0.513$, $p=0.014$). No correlation was found between $^{99m}$Tc-Tetrofosmin L/N ratio and FA ratio ($p=0.07$). Significant negative correlation was found between the ADC ratio and rCBV ($\rho=-0.538$, $p=0.01$), and marginal correlation between rCBV and FA ratio ($\rho=0.423$, $p=0.049$) but no association between ADC ratio and FA ratio ($p=0.14$).
Fig. 2: A 52 year-old male patient with a glioblastoma. A. Contrast-enhanced T1-weighted magnetic resonance (MR) image. B. Relative cerebral blood volume (rCBV) map, the rCBV value was 5.2. C. Apparent diffusion coefficient (ADC) map showing irregularly shaped enhancing lesion with perifocal oedema. The ADC ratio was 1.42. D. The co-registered fractional anisotropy (FA) maps from diffusion tensor imaging (DTI). The FA value was 0.17. E. Brain single-photon emission computed tomography (SPECT) demonstrating increased 99mTc-Tetrofosmin uptake [lesion-to normal ratio (L/N) =10]. F. Immunohistochemistry: The Ki-67 was 30% (x 400).

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Fig. 3: A 33 year-old female patient with a diffuse astrocytoma. A. Contrast-enhanced T1-weighted magnetic resonance (MR) image. B. Relative cerebral blood volume (rCBV) map. The rCBV value was 0.5. C. Apparent diffusion coefficient (ADC) map. The ADC ratio was 2.08. D. The co-registered fractional anisotropy (FA) maps from diffusion tensor imaging (DTI). The FA value was 0.2. E. Brain single-photon emission computed tomography (SPECT) demonstrating low 99mTc-Tetrofosmin uptake [lesion-to normal ratio (L/N) =1.8]. F. Immunohistochemistry: The Ki-67 index was 2% (x 400).

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Conclusion

In conclusion, the present study showed that the findings on perfusion MRI and brain SPECT with $^{99m}$Tc-Tetrofosmin were most closely correlated with glioma proliferation, as assessed by Ki-67 index. DTI also showed promise for evaluating glioma proliferation, but was inferior to both perfusion MRI and brain SPECT. Future studies with larger number of patients that will also allow for comparison of MR spectroscopy with the latest PET tracers, such as MET, are needed.
References


