Post – Treatment Neuroimaging in CNS neoplasms

One of the most frequent uses of magnetic resonance imaging (MRI) since its introduction has been in the assessment of the CNS for neoplasm.

The morphologic assessment of CNS neoplasms is based on the WHO classification. The new WHO classification is best presented by James G. Smirnotopoulos MD from the Uniformed Services University of Health Sciences in Bethesda and can be visited via the following link:

http://rad.usuhs.mil/rad/neuroradiology.html

MRI, due to its perfect soft tissue contrast and sensitivity for cerebral lesions plays to most important role for the radiologist.

However, whereas MRI initially focused on the superb contrast and spatial resolution in the brain to enable detailed morphological analysis, recent developments have focused on evaluating these in conjunction with additional functional assessments. The functional assessment of neoplasm has long been the domain of positron emission tomography (PET).

However, while PET has significantly improved our pathophysiological understanding of the CNS, the availability of MRI contrast agents and improved MR rapid imaging sequences are now enabling further assessments. Functional information can reflect macrovasculature, the breakdown of the blood brain barrier (BBB) with resulting permeability for the contrast agent, and tissue perfusion. Neurofunctional magnetic resonance imaging (nfMRI) is a recently established technique which increases our diagnostic potential in neurosciences, while MR-spectroscopic techniques such as chemical shift imaging (CSI) allow a metabolic analysis.
The diagnostic aim of functional neuroimaging of CNS neoplasm is to optimise tumour characterisation, with an emphasis on improved specificity to separate benign from malignant features. Specific characterisation facilitates planning of the most appropriate treatment. Furthermore, functional neuroimaging of CNS neoplasms can be expanded to the monitoring of ongoing therapy. The predictive assessment of therapy response and the monitoring of ongoing therapy to guide therapeutic intervention, are major challenges in the current treatment of CNS neoplasms. We focus this report on our current use of different functional neuroimaging methods for the detection and monitoring of neoplasms and their therapeutic interventions.

Post-Treatment Pseudophenomena has made conventional imaging with gadolinium contrast agent almost obsolete necessitating mechanistic techniques to differentiate entities such as pseudoprogression which is seen more commonly as a result of advanced multimodal therapeutic concepts. Advanced, non enhanced and contrast enhanced MR imaging techniques include MR-spectroscopy, perfusion MR imaging, dynamic contrast enhanced MRI and diffusion tensor MR. In the presentation we will analyse the application of those techniques in brain tumor assessment with focus on the posttherapeutic brain to differentiate therapy induced from tumor induced changes. The results of the available studies in literature, all with relatively limited patient numbers, indicate that the combination of functional MRI proved to be useful in the posttherapeutic workup of gliomas, lymphomas and metastatic disease. The typical patterns of tumor recurrence and the different therapy induced effects will be presented.

In perfusion (DSC-MRI) and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) the signal intensity measurements of the tumor reflect a composite of tumor perfusion, vessel permeability, and the extravascular-extracellular space. In contrast to conventional enhanced MRI, which simply presents a snapshot of enhancement at one time point, both techniques permits a fuller depiction of the wash-in and wash-out contrast kinetics within tumors, and this provides insight into the nature of the bulk tissue properties on its microvascular level.

With the strong demand in drug development the identification of biomarkers that can assess tumor microvascular properties non-invasive dynamic MRI is the method of choice to assess tumor response and to identify atypical tumor response findings.
Functional neuroimaging methods

The standard imaging protocol for CNS neoplasm consists of conventional spin-echo or fast spin-echo T1- and T2-weighted sequences, pre-contrast time of flight MR angiography as well as post-contrast T1-weighted spin-echo or fast spin-echo images and T1-weighted sequences with magnetisation transfer contrast. Different functional neuroimaging techniques may then be implemented on the basis of the findings obtained during standard imaging:

T1-weighted contrast-enhanced dynamic imaging

This technique can be applied only to lesions in which there is an exchange of contrast medium between the intravascular and the interstitial space [6]. Two factors influence the resulting signal enhancement: the vascular density and the vascular permeability for the contrast agent. These features are made use of for the improved characterisation of lesions, especially for the diagnostic differentiation of malignant from benign lesions. Dynamic imaging could be performed using a saturation recovery TurboFLASH (SRTF) sequence. The preparation period preceding the FLASH imaging part \(((TR/TE/a = 10/4/12)\); field of view (FOV) = 250±270 mm; matrix size (MS) = 256 × 128 interpolated to 256 × 256; section thickness (TH) = 4 mm; number of excitations (NEX) = 1\} consisted of six non-selective 90 ° pulses, each of which was followed by a gradient spoiler pulse to dephase the actual transversal magnetisation [7]. The length of the recovery period between the preparation interval and the measurement of the dominant Fourier line of the k-space was set to \(T_{REC} = 200\) ms. The imaging volume was scanned sequentially with 5±8 imaging sections of 6.5±10.4 s. The sequence was repeated 22 times, giving a total acquisition time of 3±5 min. For the SRTF sequence, a linear relationship was established between the measured signal enhancement and the concentration of gadolinium [7, 8].

For quantification, both the dose and the application technique of the contrast agent were standardised. Infusion was started simultaneously with the measurement of the third repetition of the first imaging section. The acquired series was analysed, pixel-by-pixel, using a pharmacokinetic two-compartment model. A detailed discussion of the basic assumptions and limitations of the model can be found in previous papers [8, 9]. On the basis of this model, two tissue specific parameters can be determined by least-squares fitting of the measured signal-time curves: the amplitude A, reflecting the degree of MR signal enhancement, and the exchange rate constant k21, characterising the velocity of the signal enhancement.

To enable a visual interpretation of the dynamic MR imaging data, a reference matrix-based colour-coding scheme was used to code both the amplitude A and the exchange rate constant k21. Overlaying of the colours on the MR images allowed the functional information of contrast enhancement to be combined with the corresponding morphological tissue information. To automate this approach, we developed a workstation software package for post-processing of the dynamic images [7].

This method was used in a study of 20 patients [1] for monitoring intracranial meningiomas prior to, during, and after fractionated radiation therapy. During therapy, there was a significant (p < 0.01) dose-related increase of the pharmacokinetic exchange rate k21 accompanied by an increase of the amplitude A when compared with pre-treatment values. After therapy, in patients presenting a decreased tumour volume, there was a significant decrease (p < 0.01) of the amplitude A and a decrease of the exchange rate constant k21. In the non-responding group, the pharmacokinetic analysis revealed a decrease of the amplitude A and an increase of the exchange rate constant k21. Thus, radiotherapy leads to changes in tumour microcirculation which can be detected in the pharmacokinetic images.

Several ongoing studies are aimed at evaluating the predictive potential of this technique in other organ tumours as well as in different aspects of response monitoring [10]. Early increased vascularity detected by this technique during radiation therapy seems to indicate a better overall response [11].

**T2*-contrast-enhanced perfusion imaging**
In recent years, dynamic susceptibility contrast (DSC) MR imaging has found widespread interest because of its ability to measure cerebral haemodynamics non-invasively [12, 13]. DSC MRI allows measurement of cerebral blood volume based on the principles of the indicator-dilution theory for non-diffusible tracers [14, 15].

The passage of a rapid bolus of paramagnetic contrast agent through the cerebrovascular system is monitored by acquiring a series of T2*-weighted images. The signal-time curves are converted into concentration-time curves from which blood volumes within regions of interest (ROI) can be calculated. A relative determination of regional cerebral blood volume (rCBV) values, which is possible with the standard methodology, is sufficient for most of the current clinical applications such as the early detection of ischaemia. However, for oncological applications including follow-up studies, absolute quantifications of the rCBV and regional cerebral blood flow (rCBF) are required. These necessitate a knowledge of the arterial input function (AIF) in order to calculate the tissue response to the bolus ± based concentration-time curve [16]. There are different potential methods for determination of the AIF based on intracerebral or brain feeding arteries.

We used a double-slice technique, which allowed the simultaneous measurement of the AIF in the brain feeding arteries and tissue concentration-time curves within the brain. This enabled an absolute quantification of the blood volume [16]. From each of the two sections, 55 T2*-weighted FLASH images (TR/TE1/TE2/α = 31/15/25/10°) [16] were acquired after bolus application of gadolinium. Post processing was performed on a separate workstation.

This method is applied in the diagnostic work-up of low-grade astrocytomas since there is minimal blood brain barrier breakdown and thus no contrast enhancement. The differential diagnosis can be ischaemic infarcts. Due to tumour-induced angiogenesis, most of these low grade astrocytomas present an increased blood volume compared to the surrounding white matter [2]. Following radiotherapy, there is a reduction in intratumoural blood volume. Patients with high pretherapeutic intratumoural rCBV values have a worse outcome after radiotherapy indicating more aggressive tumour growth correlated to a higher
tumour-induced angiogenesis [17]. This DSC technique may also allow an non-invasive functional assessment of delayed radiation injury, which is based on fibrosing and occlusion of small vessels. Patients who have had whole-brain radiotherapy reveal a significantly decreased rCBV in normal brain tissue. In contrast, patients with grade II astrocytoma after conformal radiotherapy have only a relatively moderate decrease in rCBV of normal tissue after therapy. The data demonstrate a measurable sparing of normal tissues with advanced radiotherapy techniques with regard to blood volume. In another study on 25 patients [3], we determined whether pre-therapeutic measurements of rCBF and rCBV could be used to predict the response of brain metastases to radiation therapy. In addition, we studied the influence of radiosurgery on rCBF and rCBV, on brain metastases and on surrounding normal brain tissue. The results demonstrated that high pre-therapeutic rCBV seemed indicative of a poor treatment outcome. After radiosurgery, patients with tumour remission and stable disease demonstrated decreased rCBV despite a temporary tumour volume increase. This was in contrast to the increased rCBV seen in patients with tumour progression at 3 months follow-up. No effects of radiosurgery on surrounding normal brain tissue were observed.

**Diffusion imaging**

Although diffusion-weighted (DW) MR imaging has been established as a diagnostically important technique in the assessment of cerebrovascular ischaemia because it gives improved delineation of the affected tissue, its application to CNS neoplasms is still in need of assessment. Mapping of the calculated apparent diffusion coefficient (ADC) has been found to be useful for improved detection and characterisation of neoplasms [22, 23]. Currently we use a diffusion-weighted spin-echo-EPI sequence [24, 25] with high spatial and temporal resolution. This approach considerably reduces the acquisition times compared with those for diffusion-weighted spin-echo sequences [26]. The diffusion-weighted spin-echo -EPI sequence uses a TE of 121 ms, a TR of 213 ms, and a gradient strength of 0.5±21.4 mT/m to acquire 12 images with different diffusion weightings. Maps of the ADC in in vivo measurements can be displayed in grey-scale.

Pilot studies already indicate that diffusion images of neoplasms show comparable lesion delineation when compared with T2-weighted images (Fig. 5). Potentially, the diffusion coefficients might provide new informa-
tion for lesion characterisation and prognosis.

**Chemical shift imaging**

A mapping of the regional distribution of cerebral metabolites (N-acetyl-aspartate (NAA), cholines (Cho), creatine (Cr) and phosphocreatine (PCr)) in a cross-section can be realised by multivoxel techniques of localised MR spectroscopy (metabolic imaging or chemical shift imaging (CSI)). 31 P-CSI is used to assess turnover of phosphorus-containing metabolites in tumours, whereas 19 F-CSI allows monitoring of chemotherapy with fluorine-containing drugs. Spectral localisation in CSI is realised by phase-encoding gradients applied before the detection of the MRI signals [27, 28]. The measurement time for a complete CSI data set is proportional to the number of phase-encoding steps in each direction. As a result, the spatial resolution is limited, in particular when nuclei of low sensitivity are detected. More flexible methods are those, which after a single excitation, allow the simultaneous encoding of spectral as well as spatial information in one direction, e. g. by means of an EPI read-out gradient or FLASH read-out. These techniques significantly shorten the measurement time of metabolic imaging at the expense, however, of a reduced signal-to-noise ratio.

In a study of patients with meningioma, we localised the volume of interest by T 2 -weighted turbo spin-echo imaging and made assessments using a 2D 1 H CSI method (Fig. 6). The CSI technique used a double spin-echo pulse sequence (TE = 135 ms, TR = 1500 ms). Two scans were acquired with 16 × 16 phase-encoding steps yielding a nominal voxel size of 1 × 1 × 1.5 cm 3 in a measurement time of 12 min. One scan, performed without a water signal suppression pulse, provided the reference signal for molar quantification of NAA, Cho and PCr. The data were processed in the time domain using a LPSVD algorithm. While the usefulness of CSI in neuro-metabolic disease is firmly established, ongoing studies indicate benefits in the assessment of primary CNS neoplasms as well as metastatic disease. Also, metabolic imaging allows monitoring of changes in metabolism during therapy. Although this technique provides information on neuro-biochemistry, its clinical application is still hampered by technical limitations.
Books on CNS Neoplasms

Anne G. Osborn
Diagnostic Neuroradiology, Mosby 1994


Internet-Links to Brain Tumor imaging

http://rad.usuhs.mil/rad/neuroradiology.html

http://neurosurgery.mgh.harvard.edu/newwhobt.htm

http://www.tbts.org/

http://www.abta.org/
Additional References


