Advanced MR and PET imaging for the assessment of treatment response in patients with gliomas.

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Learning objectives

To show the limits of conventional magnetic resonance (MR) methods in the interpretation of treatment response in patients with gliomas. To describe the functional and molecular background of the most relevant new MR and positron emission tomography (PET) imaging methods for assessment of treatment response in patients with gliomas.
Background

Treatment response in patients with high-grade gliomas is currently performed with conventional MR imaging. A T1-weighted MR sequence with gadolinium is the main sequence to assess progression on imaging during the extensive treatment regime showing enhancement due to breakdown of the blood-brain barrier. Progression during the treatment period is seen in about half of the patients (Fink et al., 2011). When progression is seen on imaging, a major clinical problem arises (Brandsma et al., 2008). Progression on conventional imaging can be the result of tumour growth and thus a failure of treatment. On the other hand, it can also occur due to treatment effects. Both effective treatment and tumour progression thus can result in breakdown of the blood-brain barrier and appear similar on imaging (Figure 1). Thus, T1-weighted MR with gadolinium has substantial limitations.

The distinction between treatment induced imaging progression and true tumour progression is possible by acquiring histology. This is not routine performed due to the invasiveness of this method. Furthermore, a non-invasive distinction can be made by acquiring follow-up MR images. If follow-up MR imaging shows a reduction or stabilisation of the imaging progression the diagnosis of treatment induced imaging progression can be made in retrospect. In the mean time, a decision about continuation or discontinuation of the heavy treatment for individual patients can not be made.

In this poster, we will show advanced MR and PET imaging methods that aid in the differentiation of treatment effects and tumour progression.
Fig. 1: Figure 1 - Tumour progression (A) en treatment induced imaging changes (B) on conventional MR T1 scans with contrast. In patient A and B is direct postoperatively no tumour visible. A new enhancing lesion is seen at the 3 months follow-up scan. At that moment, differentiation between tumour progression and treatment induced imaging changes is not possible. At the 6 months, patient A shows a clear progression of contrast enhancement consistent with tumour progression. The enhancement completely disappeared in patient B as result of treatment induced changes.

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Findings and procedure details

T1-weighted MR with gadolinium is not able to reliably discriminate between tumour progression (Figure 1A) and treatment changes (Figure 1B) in patients with high-grade gliomas. There are many tumour aspects occurring in high grade gliomas. These biological aspects of tumour can be shown with advanced function MR and PET imaging methods.

Diffusion-weighted MR can be employed to demonstrate the high cell density of tumour. Tumour-induced neovascularisation is demonstrated by perfusion-weighted MR. MR spectroscopy shows altered metabolites with an increased choline and low N-acetylaspartate. PET is able to visualize the aminoacid metabolism with $^{11}$C-MET-PET and can show an increased cell proliferation with the use of $^{18}$F-FLT-PET.

Diffusion weighted imaging

Diffusion with random direction, isotropy, occurs in the absence of barriers. A restricted diffusion occurs due to barriers. Intracellular water is less able to diffusion in comparison to extracellular water due to restriction of the cellular content, including the cell membrane (Figure 2). The high cellularity of tumour results in a lower diffusion, or diffusion restriction (Hein et al., 2004). The apparent diffusion coefficient (ADC) estimates the mean diffusivity of water molecules within each voxel (in mm$^2$/s).

Tumours demonstrate high cellularity due to the proliferation of the tumour cells. The resulting diffusion restriction is a biological reflection of this cellularity and is correlated with the ADC values (Sugahara et al., 1999). Several other effects can disturb the reliability the tumour identification. Most importantly fibrosis can show low ADC values in the absence of tumour while oedema can falsely increase ADC values in the presence of tumour (Lu et al, 2004).

Perfusion-weighted imaging

Several techniques can be used to create perfusion weighted imaging. A dynamic susceptibility T2-weighted sequences with gadolinium (DSC), shows the susceptibility effects of gadolinium on the signal echo, demonstrating a signal drop due to the gadolinium. Dynamic T1-weighted images after administration of gadolinium can demonstrate perfusion due to relaxation differences (DCE) (Figure 3). Most common used parameters are the relative cerebral blood volume (rCBV), cerebral blood flow (CBF) and time to peak (TTP) (Dhermain et al., 2010).
High grade gliomas are highly vascularised tumours with the formation of pathological blood vessels and an increased blood flow as demonstration of their aggressive behaviour. These abnormal blood vessels show an increased permeability. MRI provides a measurement of the parameters of cerebral vascularisation (Roberts et al., 2000).

**Spectroscopy**

MR spectroscopy (MRS) allows the identification of tissue metabolites. As different metabolites interfere with the magnetic signal in a different magnitude, they can be demonstrated after suppression of the abundant water signal (Figure 4).

High grade gliomas demonstrate an increase in choline and a decrease in N-acetylacetate and to a lesser degree creatine (Prat et al., 2010).

**Fluorodeoxyglucose PET**

Fluorodeoxyglucose and \(^{18}\)F-FDG is a glucose analog, which is taken up into the cell by the glucose transporter 1. Due to this mechanism, the uptake of \(^{18}\)F-FDG is seen in tissue with a high glucose metabolism, like the brain. (Figure 5).

A high background uptake of \(^{18}\)F-FDG in the brain results in a poor tumour to background differentiation. This with the fact that \(^{18}\)F-FDG is also taken up by inflammatory cells makes it a moderate test for the characterisation of brain tumour recurrence (Nihashi et al., 2013). This has resulted in research into several more accurate PET tracers.

**Methionine PET**

Cellular proliferation is associated with protein synthesis, that is composed of amino acids. The most frequently used radiolabelled amino acid is \(^{11}\)C-MET-PET. Transport of this amino acid is driven by the concentration gradient within the cell, which is dependent on the intracellular metabolism (Figure 6). Uptake of \(^{11}\)C-MET-PET thus reflects cell proliferation indirectly by the metabolic activity (Glaudemans et al., 2013). A disadvantage of \(^{11}\)C-MET-PET is the short half-life of about 30 minutes.

High-grade gliomas demonstrate high uptake of methionine due to the active metabolism of the tumour cells. Treatment effect causes only a minimal uptake due to the passive diffusion of the broken blood-brain barrier (Glaudemans et al., 2013). This make \(^{11}\)C-MET-PET a suitable tracer to differentiate tumour recurrence from treatment effects (Glaudemans et al., 2013).
**Fluorothymidine PET**

Fluorothymidine (\(^{18}\)F-FLT) is an analog of the nucleoside thymidine. Transport of \(^{18}\)F-FLT from the blood into cells is active. Once in the cell, \(^{18}\)F-FLT is a substrate for thymidine kinase, which is proportional to the cellular proliferation (Figure 7) (Herholz et al., 2012).

Cell proliferation is a highly valuable method of demonstrating tumour activity, which is the area that \(^{18}\)F-FLT is used in. Unfortunately, unlike \(^{11}\)C-MET, the breakdown of the blood-brain barrier shows pronounced leakage of FLT as well, which diminished the value of \(^{18}\)F-FLT in the differentiation of tumour recurrence and treatment effect (den Hollander et al., 2014).

**Fluro-L-DOPA PET**

Fluro-L-DOPA (\(^{18}\)F-L-DOPA) is primarily evaluated to study the dopaminergic system. However, as an amino acid analogue, it might be of value due to the similar mechanism as \(^{11}\)C-MET-PET. Cell proliferation in tumour can be indirectly displaced due to the amino acid metabolism (Figure 8) (Beuthien-Baumann et al., 2003).

The uptake of Dopamine within the normal brain tissue is low with exception of the basal ganglia. The background-tumour ratio is thus sufficient. Although Dopa-PET has demonstrated its value in characterizing of primary brain tumours, it is less specific for recurrent lesion after treatment (Fueger et al., 2010). The value of Dopa-PET in distinguishing tumour recurrence from treatment effects has not been sufficient investigated (Calabria et al., 2012).

**Cases**

We showed the limited value of conventional MRI (Figure 1). We now will show several cases of advanced MRI sequences demonstrating their use in monitoring treatment response (Figure 9-12). Although useful, they can be false-positive (Figure 11). We showed the limited value of FDG PET in brain tumour (Figure 13) and the successful use of other PET tracers (Figure 14-17).
Fig. 2: Figure 2 - Diffusion in an area with little restriction results in high diffusion (A). A diffusion weighted sequence is able to measure signal difference at the begin (b0) and the signal after a certain time (often around b1000). An apparent diffusion coefficient is then calculated from these images. Diffusion in a area with large cellularity as in tumour causes many obstacle for the diffusion (B). As result, a low diffusion, diffusion restriction is shown. A diffusion restriction is shown as a high signal on the DWI and a low signal on the ADC.

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**Fig. 3:** Figure 3 - Dynamic perfusion images are obtained with a dynamic contrast enhanced (DCE) or dynamic susceptibility contrast-enhanced (DCE) technique. The obtained curve can be used to calculate perfusion parameters as cerebral blood flow, cerebral blood volume and time to peak. Tumour (thick line) demonstrate a rapid increased in blood flow and wash out. Normal brain tissue (thin line) shows a limited slow increase in blood flow.

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Fig. 4: Figure 4 - Spectroscopy identifies metabolites by their different influence on the signal. Tumour (thick line) in comparison with normal tissue (thin line) shows an increase in choline (cho) and a decrease in N-acetyl-asetaat (NAA) and to a lesser degree creatine (crea).

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**Fig. 5:** Figure 5 - The mechanism of fluorodeoxyglucose (FDG) is illustrated. The uptake of FDG in the cancer cell is facilitated by a glucose transporter. FDG is phosphorylated by hexokinase resulting in FDG-6-phosphate. As further metabolism is not possible, FDG-6-phosphate is retained in the cell.

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**Fig. 6:** Figure 6 - The pathway of methionine (MET) in a cancer cell is schematic demonstrated. The uptake of MET in a cell is facilitated by a neutral amino acid transporter. MET is further synthesised during cell proliferation, which results in the necessary elements.

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**Fig. 7:** Figure 7 - Fluorothymidine (FLT) is an analog of the nucleoside thymidine. Transport of FLT from the blood into cells is active with a tyamine kynase 1 enzyme (TK-1). Once in the cell, FLT is a substrate for thymidine kinase, which is proportional to the cellular proliferation and thymine production.

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**Fig. 8:** Figure 8 - Dopamine (DOPA) PET can demonstrate cell proliferation in tumour indirectly due to the amino acid metabolism. Dopa uptake is done by a L-type amino acid transporter decarboxylase result in F-Dopa analog (FDA). FDA is entrapped within the cell.

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**Fig. 9:** A 29 year old female was referred from another hospital with a histology proven glioblastoma multiforme to discuss the option of neurosurgery. MRI nicely demonstrated the known glioblastoma multiforme with characteristic sign of oedema (T2), irregular peripheral enhancement with gadolinium (T1+c), diffusion restriction on the edges and no diffusion restriction centrally fitting central necrosis (DWI and ADC), increased perfusion (rCBV) and increased choline with an elevated lactae.

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**Fig. 10:** A 23 year old female was referred to the hospital for headache in the morning and a reduced strength and coordination on the left side objectivised with physical exam. An MRI was performed to evaluate the option of a structural brain lesion. MRI demonstrated a tumour in the region of the right thalamus, probably a high-grade glioma. Biopsy proved it to be a glioblastoma multiforme. Surgery was performed after multidisciplinary consultation with a partial resection. Radiotherapy and temozolomide was started and follow-up with MRI was performed. Lesion growth was demonstrated at the 6 months follow-up MRI with characteristic sign of tumour growth. Peripaeral rim enhancement with areas with diffusion restriction, and necrosis as well as areas with increased perfusion and increased choline values were demonstrated.

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Fig. 11: A 60 year old male was monitored after a glioblastoma multiforme resection direct after radiotherapy. MRI demonstrated enhancement at the resection site. Although diffusion demonstrate some restriction, perfusion imaging was normal. The pattern of enhancement together with the normal perfusion made a radiotherapy effect most likely. This was confirmed during follow-up as MRI three months later demonstrated reduction of the enhancement, persistent diffusion restriction and normal perfusion imaging. Further follow-up (for one year) also confirmed that the enhancement direct post radiotherapy was a treatment effect and no true tumour progression. Diffusion demonstrated to be false-positive is this specific patient.

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Fig. 12: A 64 year old male was monitored after a surgical resection and radiotherapy of a facial squamous cell carcinoma. The patient experienced some behavioural changes. MRI three year after the end of radiotherapy demonstrated increased enhancement on T1 images with contrast. Diffusion was only focally restricted at the genu of the corpus callosum. Perfusion MRI demonstrated no increased vascularisation. Multidisciplinary consultation indicated that radionecrosis would be the most likely diagnosis. Follow-up MRI images (for example 4 years later) were persistent with the diagnosis of radionecrosis with reduction of the enhancement, no diffusion restriction and no enhanced perfusion. The patient died 4 years after the initial MRI probably due to a myocardial infarction.

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**Fig. 13:** Figure 13 - A 62 year old female was monitored after a fluorodeoxyglucose (FDG) PET scan for metastases of a small cell lung cancer. The FDG demonstrated possible decreased cerebral uptake. MRI performed a few days later demonstrated clearly enhancing tumour localisations. Multiple areas were not visible on FDG imaging (for example see red arrow). No clear diffusion restriction was seen which also could be seen in case of abscesses. This case demonstrates the lack of diagnostic sensitivity of a FDG-PET scan for brain tumours. We therefore do not perform FDG-PET scans in patients with a glioblastoma multiforme.

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**Fig. 14:** Figure 14 - A 62 year old male was monitored after a glioblastoma multiforme resection 3 months earlier. MRI demonstrated avid enhancement at the resection site. An additional methionine (MET) PET was performed and successfully excluded a treatment effect as reason for the enhancement. Stereotactic radiotherapy was performed. He is still alive now, 4 years later.

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Fig. 15: Figure 15 - A 43 year old male was monitored after a glioblastoma multiforme resection 9 months earlier. MRI demonstrated avid enhancement at the resection site. An additional MET-PET was performed and successfully demonstrating uptake making the diagnosis tumour progression more likely. He died 10 months after the MET-PET scan.

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**Fig. 16:** Figure 16 - A patient was monitored after primary glioblastoma multiforme resection. She demonstrated uptake on fluorothymidine (FLT) PET imaging 3 months after the end of radiotherapy fitting tumour growth.

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**Fig. 17:** Figure 17 - A 26 year old female was monitored after a glioblastoma multiforme resection 5 months earlier. MRI demonstrated some enhancement anterior of the resection site. Diffusion MRI showed no diffusion restriction and perfusion MRI showed no elevated perfusion (rCBV). A definitive diagnosis was not possible at this stage. A additional dopamine (DOPA) PET scan for evaluation of parkinsonian symptoms was performed a few weeks later. Elevated uptake was shown at the site of enhancement on MRI, suggestive of tumour recurrence. Follow-up MRI confirmed this, showing tumour growth. The patients deceased within a year after the DOPA-PET scan.

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Conclusion

Conventional T1-weighted MR with gadolinium is the standard for assessment of treatment response in patients with gliomas. However, it should be interpreted with caution. Multimodal advances MR and PET methods provides new opportunities to adequate assess treatment response, adding in the therapeutic decision. This includes changes in diffusion reflecting cell density (diffusion-weighted MR), tumour-induced neovascularisation (perfusion-weighted MR), metabolite changes as increased choline (MR spectroscopy), increased aminoacid metabolism ($^{11}$C-MET-PET and DOPA-PET) and increased cell proliferation ($^{18}$F-FLT-PET) (Figure 18).

Individually, these techniques have shown their potential usefulness for the assessment of treatment response. Combination of these techniques is promising for differentiation between tumour progression and treatment changes. Especially, hybrid PET-MRI scanners offers the potential for robust combined structural, functional and molecular imaging assessment. Further research is needed to define and standardise cutoff values and optimum time for assessment of MR and PET variables in relation to treatment effects and patient outcomes.
Fig. 18: Figure 18 - Advanced MR sequences (A-D) and PET tracers (E-H) aid to identify tumour progression. Tumour is indicated by tumour-induced vascularisation by perfusion-weighted MR (A), increased cellularity inducing diffusion restriction (B), elevated choline (C-D), elevated metabolism with increased MET-PET uptake (E) and DOPA-PET uptake (G) and increased cell proliferation with FLT-PET (F). FDG-PET is of limited value (H).

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