

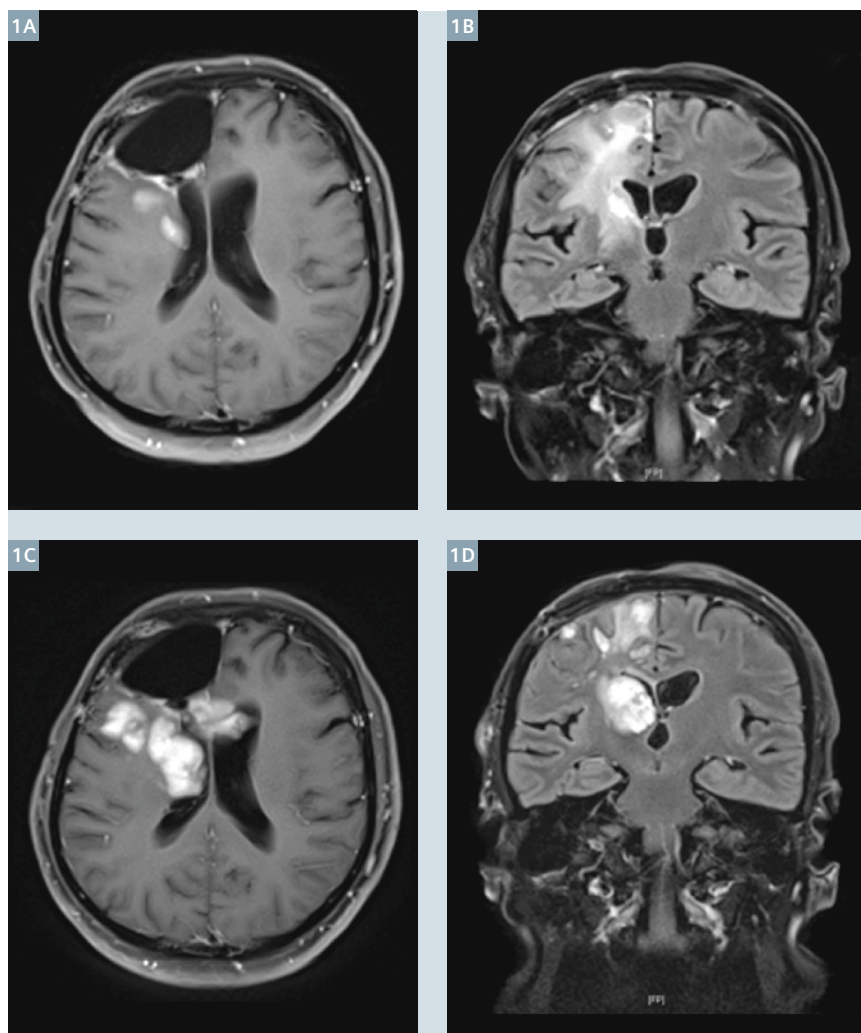
# Clinical Application of Diffusion Tensor Imaging in Radiation Planning for Brain Tumors

S. Rogers<sup>1</sup>; S. Bodis<sup>1</sup>; G. Lutters<sup>1</sup>; L. Remonda<sup>2</sup>; J Berberat<sup>1, 2</sup>

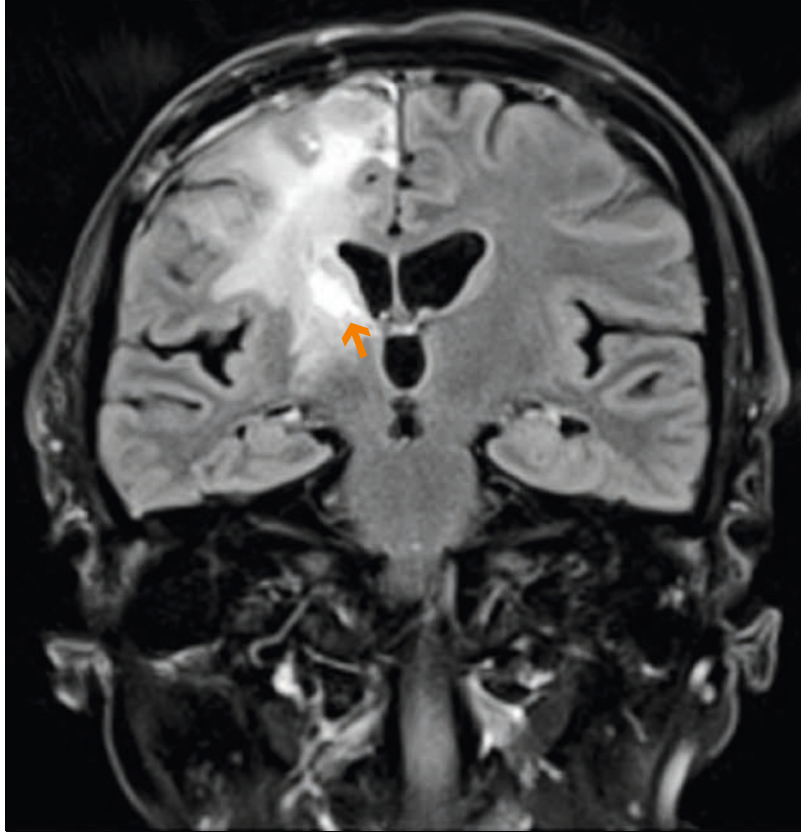
<sup>1</sup>Radiation Oncology, Canton Hospital, Aarau, Switzerland

<sup>2</sup>Neuro-radiology, Canton Hospital, Aarau, Switzerland

Malignant brain tumors (glioma WHO grade III-IV) are notoriously difficult to treat despite an intensive combination of surgery, radiation and chemotherapy. Although there is an increasing number of 5-year survivors with this combined modality therapy, the median survival remains in the order of 14 months [1]. Pathological studies have demonstrated preferential tumor cell dissemination spread along white matter tracts and brain vessels [2], which limits the efficacy of both microsurgical resection and radiation therapy. The target for post-operative therapeutic radiation after maximal safe resection includes the resection cavity and any residual tumor visible on the postoperative T1-weighted Gadolinium-enhanced MRI. When surgery is not possible due to a high risk of neurological damage, a diagnostic biopsy is undertaken, followed by radiotherapy. To maximise the probability of including relevant microscopic spread from a glioblastoma (glioma WHO grade IV), uniform wide planning margins of up to 30 mm are typically added (Fig. 2B, green line). Some centres further extend this to include all visible edema on the T2-weighted imaging. Recent studies on the pattern of relapse in patients with high-grade glioma (HGG), predominantly glioblastoma, have suggested that tumor recurrence after maximal combined modality therapy occur within 2 cm of the original tumor location [3, 4]. This has led to a suggestion that a



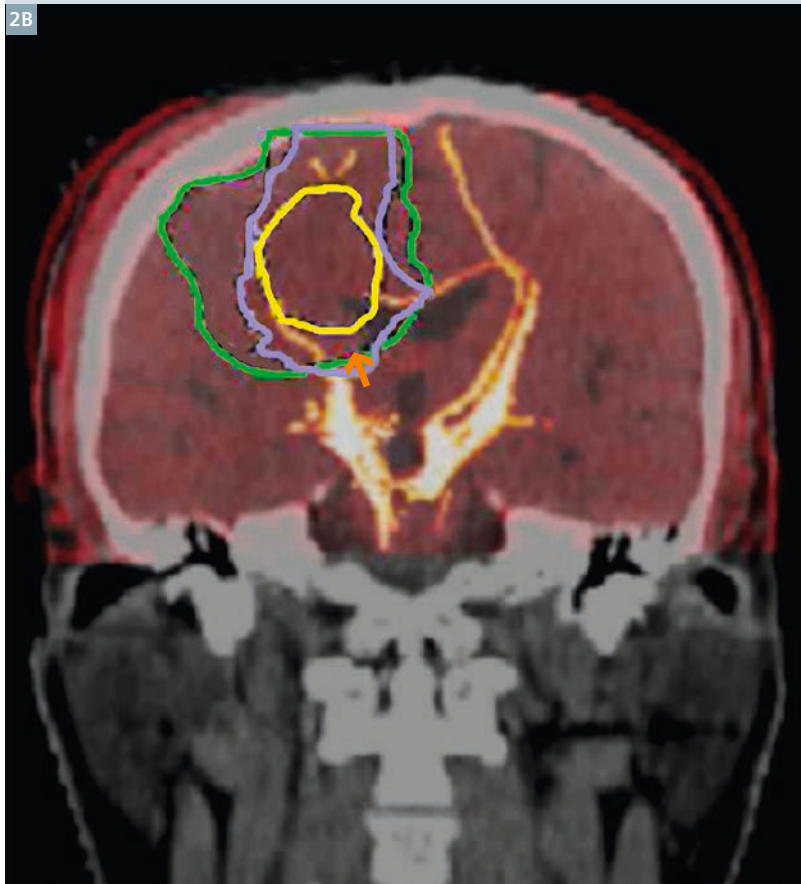
**1** Transverse (T1w BLADE fs) and coronal (T2w TIRM dark fluid fs) MR images (1A, B) 12 months and (1C, D) 16 months after the operation. The patient developed a progressive tumor recurrence contiguous with residual tumor with subsequent extension along neighboring white matter tracts.



reduced margin, for example 1 cm, may be sufficient for the high-dose volume [3].

The addition of temozolomide chemotherapy as a radiation sensitizer and as adjuvant therapy is reported to be associated with an increased risk of normal brain toxicity (radionecrosis) of up to 20% [5]. Radiation-related side effects are dependent on both the prescription dose and the irradiated volume. A dose of at least 60 Gy has been shown to be necessary to control HGG, therefore it is compelling to instead reduce the planning target volume (PTV) where possible without compromising efficacy. Our aim is to derive a biologically targeted volume to ensure coverage of the regions at greatest risk of microscopic infiltration whilst excluding uninvolved brain. To this end, we have explored diffusion tensor imaging (DTI) and fractional anisotropy (FA) to identify areas of tumor infiltration, beyond that visible on T1w contrast-enhanced MRI. The method is derived from the isotropic (p) and anisotropic (q) maps of water diffusivity [6] and based on clinically validated data from patients with HGG [7].

Our technique is best illustrated using a clinical case as an example. This patient with histologically confirmed glioblastoma (GBM), showed tumor progression after surgery and radiation and developed a new lesion in the right thalamus (Fig. 1). The initial pre-operative work-up included DTI to assist the neurosurgeons in the identification and avoidance of apparently uninvolved white matter tracts to minimize the neurological sequelae of the surgery. All the MR imaging was done using a MAGNETOM Avanto 1.5T whole body scanner (Siemens Healthcare, Erlangen, Germany). These same scans were further analysed to extract data



Fusion of the MRI at recurrence 12 months post op with the DTI at recurrence 12 months post op suggests a route of spread via the radiologically abnormal right corticospinal tract.

regarding water diffusivity. The initial steps of the radiation planning technique were to co-register the T1w contrast-enhanced MRI with the planning CT scan. The residual enhancing tumor was contoured accordingly and the volume expanded by 1 cm (Fig. 2B, yellow line) to include brain at highest risk of infiltration. In addition, the DTI scan was co-registered and the volume was extended further along the tracts (Fig. 2B, purple line) in contact with the tumor to encompass likely microscopic spread. Any additional regions of tumor and infiltration, as detected by the p and q

maps, were delineated and then combined into the target volume by the planning software. This final volume was used to generate intensity modulated radiotherapy (IMRT) plans that were not used for clinical treatment (Fig. 2).

Using an in-house software program, we have developed a technique to incorporate regions of altered water diffusivity, reported to correspond with macroscopic tumor or microscopic infiltration, into the radiotherapy planning process. Conventional large volume irradiation for high-grade glioma carries an inevitable

risk of neuro-toxicity, which may be enhanced by combination with radiosensitizers. DTI and FA have previously been reported as diagnostic tools to assist with differential diagnosis, tumor grading, identifying tumor margins and predicting tumor relapse [7-9]. As white matter tracts and alterations in water diffusivity can also be targeted, we believe that future developments in radiation planning for HGG should endeavour to reduce the irradiated volume whilst maintaining adequate coverage of such regions likely to mediate relapse and spread.

## References

- 1 Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009 10(5):459-66.
- 2 Giese A, Westphal M. Glioma invasion in the central nervous system. *Neurosurgery* 1996 39(2):235-50.
- 3 McDonald MW, Shu HK, Curran WJ Jr, Crocker IR. Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. *Int J Radiat Oncol Biol Phys* 2011 1;79(1):130-6.
- 4 Milano MT, Okunieff P, Donatello RS, Mohile NA, Sul J, Walter KA, Korones DN. Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2010 15;78(4):1147-55.
- 5 Rusthoven KE, Olsen C, Franklin W, Kleinschmidt-DeMasters BK, Kavanagh BD, Gaspar LE, Lillehei K, Waziri A, Damek DM, Chen C. Favorable prognosis in patients with high grade glioma with radiation necrosis: the University of Colorado experience. *Int J Radiat Oncol Biol Phys*. 2011 1;81(1):211-7.
- 6 Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 1994 103(3):247-54.
- 7 Price SJ, Jena R, Burnet NG, Hutchinson PJ, Dean AF, Peña A, Pickard JD, Carpenter TA, Gillard JH. Improved delineation of glioma margins and regions of infiltration with the use of diffusion tensor imaging: an image-guided biopsy study. *AJNR Am J Neuroradiol* 2006 27(9):1969-74.
- 8 Byrnes TJ, Barrick TR, Bell BA, Clark CA. Diffusion tensor imaging discriminates between glioblastoma and cerebral metastases in vivo. *NMR Biomed* 2011 24(1):54-60.
- 9 Mohsen LA, Shi V, Jena R, Gillard JH, Price SJ. Diffusion tensor invasive phenotypes can predict progression-free survival in glioblastomas. *Br J Neurosurg* 2013 27 [Epub ahead of print].

## Contact

Jatta Berberat, Ph.D.  
Canton Hospital  
Tellstrasse  
5001 Aarau  
Switzerland  
jatta.berberat@ksa.ch