Clinical Oncology (2005) **17**: 581–590
doi:10.1016/j.clon.2005.04.012

Original Article

Diffusion Tensor Imaging: Possible Implications for Radiotherapy Treatment Planning of Patients with High-grade Glioma

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ABSTRACT:
Aims: Radiotherapy treatment planning for high-grade gliomas (HGG) is hampered by the inability to image peri-tumoural white-matter infiltration. Diffusion tensor imaging (DTI) is an imaging technique that seems to show white-matter abnormalities resulting from tumour infiltration that cannot be visualised by conventional computed tomography or magnetic resonance imaging (MRI). We propose a new term, the image-based high-risk volume (IHV) for such abnormalities, which are distinct from the gross-tumour volume (GTV). For IHV based on DTI, we use the term IHV_{DTI}. This study assesses the value of DTI for the individualisation of radiotherapy treatment planning for patients with HGG.
Methods: Seven patients with biopsy-proven HGG were included in a theoretical planning exercise, comparing standard planning techniques with individualised plans based on DTI. Standard plans were generated using a 2.5 cm clinical target volume (CTV) margin added to the GTV. For DTI-based plans, the CTV was generated by adding a 1 cm margin to the IHV_{DTI}. Estimates of normal tissue complication probability (NTCP) were calculated and used to estimate the level of dose escalation that could be achieved using the DTI-based plans.
Results: The use of DTI resulted in non-uniform margins being added to the GTV to encompass areas at high risk of tumour involvement, but, in six out of seven cases, the IHV_{DTI} was encapsulated by the standard CTV margin. In all cases, DTI could be used to reduce the size of the planning-target volume (PTV) (mean 35%, range 18–46%), resulting in escalated doses (mean 67 Gy, range 64–74 Gy), with NTCP levels that matched the conventional treatment plans.
Conclusion: DTI can be used to individualise radiotherapy target volumes, and reduction in the CTV permits modest dose escalation without an increase in NTCP. DTI may also be helpful in stratifying patients according to the degree of white-matter infiltration. Jena, R. *et al*. (2005). *Clinical Oncology* **17,** 581–590
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Key words: Diffusion tensor imaging, dose escalation, gliomas, radiotherapy

Received: 6 January 2005 Revised: 26 April 2005 Accepted: 27 April 2005

Introduction

The tendency for high-grade gliomas (HGG) to spread insidiously into surrounding brain tissue is a key factor in the aggressive clinical nature of these tumours. Patients who are fit and without neurological deficit are usually offered post-operative radical radiotherapy. Since the late 1970s, especially after the work by Walker *et al.* [1], 60 Gy has been a standard radical dose for HGG around the world [1]. The superiority of 60 Gy over 45 Gy as a radical treatment dose for HGG was confirmed in the UK by the 1991 MRC study [2]. This study of two dose schedules showed that radical radiotherapy treatment at doses of 60 Gy prolongs median survival for these patients. Nevertheless, for unselected patients with glioblastoma, only about 3% achieve long-term tumour control.

Advances in radiotherapy have led to interest in attempts at dose escalation for HGG. A variety of techniques, including stereotactic boost, proton beam therapy, brachytherapy, and intensity-modulated radiotherapy (IMRT) have been used [3–8]. A few small retrospective studies have shown modest improvements in median survival, in the region of 3–15 months. Although doses in the region of

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0936-6555/05/000000+10 $35.00/0
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90 Gy were able to sterilise 30% of tumours in one study [4], in general, most patients develop tumour recurrence. Two studies have recently examined the pattern of relapse in relation to radiotherapy treatment volumes [9,10]. In both studies, most tumours recurred in the high-dose treatment volume, rather than at the margin or at distant sites. These findings are consistent with earlier data, from the early era of computed tomography (CT) imaging, which formed the basis for the margin for clinical target volume (CTV) [11]. These studies suggest that local tumour recurrence may not be caused by inadequate treatment volumes, but that the dose to the central tumour is insufficient to maintain tumour control [9].

Previous studies of dose escalation have made no attempt to individualise the treatment volume according to biological growth characteristics of the underlying tumour. This is largely because standard CT and magnetic resonance imaging (MRI) are unable to demonstrate sub-clinical tumour spread. Diffusion tensor imaging (DTI) is an MRI technique that is sensitive to changes in water diffusion in white-matter tracts. Earlier work from our group has shown that defects in white-matter tracts can be identified, which seem to correlate with tumour spread [12]. These abnormalities could not be detected on standard T_2-weighted or Gadolinium-enhanced magnetic resonance sequences. We have also demonstrated that deconvolution of diffusion tensor data into isotropic and anisotropic components allows the production of tissue 'signatures', which can distinguish between infiltrated and normal white matter [13].

The dose of radiotherapy that can safely be administered is considered to be inversely related to the volume of brain in the irradiated volume [14]. Clinical data suggest that reduction in the volume of irradiated normal brain improves both acute and late side-effects [15,16]. Given that HGG typically show a pattern of central recurrence, decreasing the volume of irradiated brain would allow a larger dose to be delivered to the tumour without increasing the risk of normal tissue complication. On the basis that DTI might image sub-clinical tumour invasion, we hypothesise that this new imaging technique could be used as the basis for individualised radiotherapy planning for HGG, according to the tumour growth characteristics of each individual patient. By reducing the CTV margin in areas showing no evidence of white-matter invasion, a reduction in the target volume could be achieved. Such a strategy would permit individualisation of the CTV for radiotherapy treatment plans. We describe a theoretical planning exercise, designed to assess the feasibility of DTI, as a tool for individualisation of treatment volume and dose compared with standard planning techniques.

Methods

This dosimetry study was undertaken to test the hypothesis that DTI could be used as the basis of a dose-escalation strategy. None of the DTI-based plans produced in the study were used for clinical treatment.

Patient Identification and Selection

Patients with a biopsy-confirmed diagnosis of high-grade glioma were identified at the neuro-oncology multidisciplinary review meeting at Addenbrooke's Hospital, Cambridge. Patients who were deemed fit for radical radiotherapy treatment (WHO performance status 0 or 1), and with no contraindication to MRI, were invited to undergo DTI and conventional MRI before radiotherapy treatment. Recruitment was carried out by members of the study team in the Neuro-Oncology Unit and the Department of Neurosurgery at Addenbrooke's Hospital. Written informed consent was obtained from all patients who were recruited from studies approved by the Local Research Ethics Committee. Data were available for seven patients (three men, four women, mean age 44 years, age range 23–59 years) for inclusion in this dosimetry study.

Imaging Sequences and Processing

MRI was carried out at 3 Tesla (Bruker, Etlingen, Germany). All patients were imaged in the axial plane with 4-mm-slice thickness and using a 1-mm-interslice separation. Imaging consisted of T_2/proton density fast spin echo sequence (repetition time (TR) = 6055 ms; echo time (TE) = 80 ms/20 ms; field of view (FOV) = 35.84 × 16.8 cm; matrix 512 × 256; 27 slices), and a single-shot, spin echo, echo planar diffusion tensor sequence (TR = 5070 ms; TE = 107 ms; FOV 25 × 25 cm for eight slices, 19.5 × 19.5 cm for 27 slices; matrix 128 × 128; between eight and 27 slices). Each slice from the DTI sequence was collected from 12 non-colinear gradient directions. For each direction, one T_2 (b_0) image and five diffusion gradient weighted images were collected (318 s/mm^2, 392.5 s/mm^2, 785 s/mm^2, 1177.5 s/mm^2 and 1570 s/mm^2).

In order to calculate the diffusion tensor on an individual voxel basis, a solution to the Stejskal–Tanner equation was required. This was implemented using an in-house MATLAB script (The Mathworks, Natick, USA) according to the technique described by Basser *et al.* [17]. Diffusion tensor data were visualised by calculating fractional anisotropy maps, demonstrating the magnitude of diffusion in the principal eigenvector. These maps give excellent anatomical images of white-matter tract location and integrity [18]. Figure 1 shows a fractional anisotropy map from a patient showing effacement of a white-matter tract due to tumour infiltration.

The resulting fractional anisotropy maps were co-registered to T_2-weighted images using the VTK registration toolkit (CISG, King's College, London). For each fractional anisotropy map, mean fractional anisotropy values were calculated for normal white matter, involved white matter and tumour. These values were used in threshold analysis to help distinguish between normal and suspicious white-matter tracts in the region of the tumour.

Both fractional anisotropy and T_2 maps were co-registered to planning CT studies using a normalised mutual information algorithm [19]. An example of the image

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