



Voxel-based clustered imaging by multiparameter diffusion tensor images for glioma grading



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ABSTRACT

Gliomas are the most common intra-axial primary brain tumour; therefore, predicting glioma grade would influence therapeutic strategies. Although several methods based on single or multiple parameters from diagnostic images exist, a definitive method for pre-operatively determining glioma grade remains unknown. We aimed to develop an unsupervised method using multiple parameters from pre-operative diffusion tensor images for obtaining a clustered image that could enable visual grading of gliomas. Fourteen patients with low-grade gliomas and 19 with high-grade gliomas underwent diffusion tensor imaging and three-dimensional T1-weighted magnetic resonance imaging before tumour resection. Seven features including diffusion-weighted imaging, fractional anisotropy, first eigenvalue, second eigenvalue, third eigenvalue, mean diffusivity and raw T2 signal with no diffusion weighting, were extracted as multiple parameters from diffusion tensor imaging. We developed a two-level clustering approach for a self-organizing map followed by the K-means algorithm to enable unsupervised clustering of a large number of input vectors with the seven features for the whole brain. The vectors were grouped by the self-organizing map as protoclusters, which were classified into the smaller number of clusters by K-means to make a voxel-based diffusion tensor-based clustered image. Furthermore, we also determined if the diffusion tensor-based clustered image was really helpful for predicting pre-operative glioma grade in a supervised manner. The ratio of each class in the diffusion tensor-based clustered images was calculated from the regions of interest manually traced on the diffusion tensor imaging space, and the common logarithmic ratio scales were calculated. We then applied support vector machine as a classifier for distinguishing between low- and high-grade gliomas. Consequently, the sensitivity, specificity, accuracy and area under the curve of receiver operating characteristic curves from the 16-class diffusion tensor-based clustered images that showed the best performance for differentiating high- and low-grade gliomas were 0.848, 0.745, 0.804 and 0.912, respectively. Furthermore, the log-ratio value of each class of the 16-class diffusion tensor-based clustered images was compared between low- and high-grade gliomas, and the log-ratio values of classes 14, 15 and 16 in the high-grade gliomas were significantly higher than those in the low-grade gliomas ($p < 0.005$, $p < 0.001$ and $p < 0.001$, respectively). These classes comprised different patterns of the seven diffusion tensor imaging-based parameters. The results suggest that the multiple diffusion tensor imaging-based parameters from the voxel-based diffusion tensor-based clustered images can help differentiate between low- and high-grade gliomas.

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Abbreviations: ADC, apparent diffusion coefficient; AUC, area under the curve; BET, FSL's Brain extraction Tool; BLSOM, batch-learning self-organizing map; CI, confidence interval; CNS, central nervous system; DTCl, diffusion tensor-based clustered image; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EPI, echo planar image; FA, fractional anisotropy; FDT, FMRIB's diffusion toolbox; FLAIR, fluid-attenuated inversion-recovery; FSL, FMRIB Software Library; HGG, high-grade glioma; KM, K-means; KM++, K-means++; L1, first eigenvalue; L2, second eigenvalue; L3, third eigenvalue; LGG, low-grade glioma; LOOCV, leave-one-out cross-validation; MD, mean diffusivity; MP-RAGE, magnetization-prepared rapid gradient-echo; MRI, magnetic resonance imaging; PET, positron emission tomography; ROC, receiver operating characteristic; ROI, region of interest; S0, raw T2 signal with no diffusion weighting; SOM, self-organizing map; SVM, support vector machine; T1WI, T1-weighted image; T1WIce, contrast-enhanced T1-weighted image; T2WI, T2-weighted image; WHO, World Health Organization.

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1. Introduction

Gliomas are the most common primary neoplasms of the central nervous system (CNS), and are classified according to a grading system, commonly that of the World Health Organization (WHO), on the basis of their histological appearance. Tumour grading is an important factor that influences the choice of therapy, such as adjuvant radiation and chemotherapy (Louis et al., 2007b).

Patients with low-grade gliomas (LGGs) (WHO grade II) may live for a long time, and the 5-year survival rate is 42%–92% (Sanai and Berger, 2008). In contrast, patients with high-grade gliomas (HGGs) (WHO grades III and IV) have a worst prognosis of brain tumours (Law et al., 2006); particularly, glioblastoma (WHO grade IV) develops rapidly (Ohgaki and Kleihues, 2007), and the 5-year survival rate is only 2% (McLendon and Halperin, 2003). Therefore, patients with HGGs need to be treated as soon as possible and more aggressively with chemotherapy and radiation. Thus, it is important to accurately classify gliomas into low or high grades to provide the best treatment for patients.

Magnetic resonance imaging (MRI) is essential for non-invasively diagnosing the existence, extent and characteristics of brain tumours. Different MRI sequences are used for evaluation and include T1-weighted image (T1WI), contrast-enhanced T1-weighted image (T1WIce), T2-weighted image (T2WI), diffusion-weighted imaging (DWI) and fluid-attenuated inversion-recovery (FLAIR) sequences. The images can provide much information about tumours, such as tumour morphology, the presence of enhancement, intra-tumoural haemorrhage or peri-tumoural oedema and can be helpful to predict tumour grade. The presence of contrast enhancement is often regarded as a sign of malignancy. Watanabe et al. reported that enhancement was present in 11 of 12 HGGs in their study, and histological examination revealed that areas of enhancement were related to neovascularity in tumour tissue or tumour cell infiltration (Watanabe et al., 1992). However, it was also reported that 9% of malignant gliomas lacked enhancement and 48% of LGGs were enhanced (Scott et al., 2002). These studies suggested that T1WIce was less useful than expected for prediction of glioma grade. Furthermore, gadolinium-based contrast agents, which are typically used in MRI, can cause side effects. Acute reactions after injection of gadolinium may cause flushing and nausea as minor reactions and hypotension and bronchospasm as intermediate reactions. In addition to these side effects, severe reactions are all symptoms of minor and intermediate reactions and sometimes cause cardiac arrest (Thomsen, 2003). Thus, T1WIce cannot be used for definitive pre-operative glioma grading because of insufficient information or side effects.

Some previous studies have used other MRI sequences without contrast agents, including diffusion tensor imaging (DTI), for glioma grading. Diffusion is sensitive to water movement, particularly along axonal fibres. DTI provides useful information about diffusion measurements and enables calculation of several parameters from DTI. Because tumour cells of gliomas mainly invade along white matter tracts (Scherer, 1938), we believe that DTI is a potentially useful sequence because of its sensitivity to white matter abnormalities (Filippi et al., 2001). Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) calculated from DTI are more sensitive indicators of the integrity of white matter and tumour infiltration than are T1WI or T2WI (Price et al., 2003). Thus, DTI parameters can have an important role in the assessment of tumours. It has been reported that compared with white matter, HGGs show a mixture of hyper- and iso-intensities in DWI (Tien et al., 1994; Stadnik et al., 2001). One study found that lower ADC values corresponded to increased cellularity and HGGs (Kao et al., 2013). However, another study found no significant difference in ADC values between LGGs and HGGs (Lam et al., 2002). The FA values of LGGs were significantly lower than those of HGGs (Inoue et al., 2005; Kao et al., 2013), whereas another study showed low FA ratios in the tumour centres of both LGGs and HGGs (Goebell et al., 2006). These previous studies suggest that glioma grading with a single parameter of MRI remains controversial.

Recently, a pattern recognition method using multiple parameters has been applied to predict tumour grading. In a study, support vector machine (SVM), which is a widely used supervised machine-learning method because of its remarkable performance of classification, was applied and involved 161 features extracted from manually defined regions of interest (ROIs) on T1WI, T1WIce, T2WI, FLAIR and perfusion MRI using a contrast agent, and a combination of multiple features that differentiated HGGs and LGGs with an accuracy of 87.8%, sensitivity of 84.6% and specificity of 95.5% was reported (Zacharaki et al., 2009). Another study used a self-organizing map (SOM) based on a competitive learning algorithm, which is a type of neural network unsupervised learning, with seven features extracted from wavelet-filtered ADC, ADC, FLAIR and T2WI for each voxel (Vijayakumar et al., 2007). SOM was labelled for seven tissue classes, including low- and high-grade tumours, in a supervised manner using 700 voxel-based training pattern vectors. Although the sample size was small (four patients with low- and six with high-grade tumours), the method differentiated low-grade tumour from other tissues, with a sensitivity of 88% and a specificity of 98%, and high-grade tumour from other tissues, with a sensitivity of 87% and a specificity of 93%. Although pattern recognition methods with multiple parameters and a supervised manner can be useful for prediction of tumour grading, they have some problems in clinical applications. In voxel-based labelling, because it is impossible to examine the pathology of each voxel, supervised voxel-based labelling can be inaccurate and cause rater bias. Furthermore, complicated features make it difficult to determine the most sensitive parameter for characterizing grading. Therefore, a pattern recognition method with multiple uncomplicated parameters without supervised information can be helpful to predict glioma grade. Furthermore, SOM is well-known to its visualization and would help to lead to a novel classification.

This study aimed to develop a new method using multiple DTI-based parameters for voxel-based clustered images in an unsupervised manner that can be used to visually grade gliomas. We also determined if the method is really helpful for pre-operative prediction of glioma grade in a supervised manner.

2. Materials and methods

2.1. Subjects

We retrospectively reviewed 111 patients who were aged 6–87 years and had newly diagnosed and histologically confirmed diffusely infiltrative gliomas, defined according to the WHO classification (Louis et al., 2007a), between March 2010 and June 2013 in Kyoto University Hospital. We classified grade II as LGG ($n = 36$) and grades III and IV gliomas as HGG ($n = 75$) in this study. Patients with LGGs had 22 diffuse astrocytomas, eight oligodendrogliomas, four oligoastrocytomas and two mixed oligoastrocytomas. Patients with HGGs had 17 anaplastic astrocytomas, three anaplastic oligoastrocytomas, two anaplastic oligodendrogliomas and 53 glioblastomas. Among these patients, 51 underwent DTI and magnetization-prepared rapid gradient-echo (MP-RAGE). We excluded 13 patients who had undergone previous tumour resections or exposures to radiotherapy or chemotherapy prior to DTI acquisition. We also excluded three patients whose tumours were located around the temporal basal regions that were severely influenced by distortions of DTI (Mangin et al., 2002) and one patient because of appreciable motion artefacts in MP-RAGE. We excluded one patient <12 years of age because FA values in the frontal white matter are significantly lower in children aged 8–12 years than in adults because of less myelination in children (Klingberg et al., 1999). Consequently, 33 patients (22 men, 11 women) were enrolled in the study. Thirty-two patients had undergone tumour resections, and one had only undergone a biopsy. Twenty-one tumours were located in the frontal region, seven in temporal, two in parietal, one in occipital and two in frontoparietal (Table 1). This study was approved by the Ethics Committee of the Kyoto University Graduate School

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