論　文　内　容　要　旨

Nonenhancing peritumoral hyperintense lesion on diffusion-weighted imaging in glioblastoma: a novel diagnostic and specific prognostic indicator

(膠芽腫周辺の造影効果を伴わない拡散強調画像高信号域：診断と特異的予後因子としての所見)

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Background and purpose

Glioblastoma is the most common malignant primary neoplasm of central nervous system (CNS) accounting for 16% of all primary intracranial tumors and 54% of all gliomas. The differential diagnosis of high grade glioma includes a variety of other intra-cranial tumors like malignant lymphomas and metastatic tumors that often pose a pre-operative diagnostic difficulty. Radiological tumoral characteristics of these clinical entities are often indiscernible.

Diffusion-weighted MRI is a molecular physiology based imaging modality which enables volumetric measurement of tissue characteristics. Previous studies have demonstrated its usefulness in diagnosis of different brain pathologies. Most studies focused on the study of tumor characteristics and a very few studies on the characteristics of peritumoral tissue. We focused mainly on the peritumoral lesion as gliomas have the propensity to potentially invade the surrounding white matter.

In this study, we focused on peritumoral white matter to establish its usefulness for differentiation of glioblastoma from malignant lymphomas and metastatic tumors and identify a feature that is efficient for its preoperative differentiation.

Methods

Patients with malignant brain tumor admitted in our institution were analyzed retrospectively after receiving approval of the Institutional review board. MR images including DWI at 3T with b=1000 s/mm^2 and b=4000 s/mm^2 were reviewed in histologically confirmed 62 patients of glioblastoma, 32 of malignant lymphoma and 46 of metastatic tumors. The area adjacent to and within 3 cm of the enhanced tumor was defined as the peritumoral region. Presence of Gd non-enhancing peritumoral DWI high-intensity lesion (NePDHL) was confirmed in both DWI sequences by two observers in consensus. DWI hyper-intensity may be due to restricted diffusion or other artifacts including T2-shine through effect in normal tissues which were excluded using ADC

maps.

Lesions were defined as “Definite” if present within 3 cm of the enhanced tumor as high-intensity with signal-intensity ratio (SIR) of ≥30% as compared to contralateral normal white matter (CNWM) in both sequences and as “Probable” if present in only one DWI sequence (SIR ≥30%) or present with SIR of <30% in both sequences compared to CNWM. In our study, setting signal intensity ratio (SIR) of DWI signal intensity at 30% had the sensitivity of 1 and specificity of 0.8 (AUC=1) and could delineate between actual hyperintensity of Definite-NePDHL and those arising due to artifacts and T2-shine through effect of normal white matter. Grey matter lesions were excluded.

All data were processed in a GE Advanced Work station and ADC maps were generated using software Functool. Regions of interest (ROIs) in enhanced tumor and Definite-NePDHL on ADC maps of b-1000 were manually placed in consensus and were repeated for ADC maps of b-4000. ADC values were expressed as minimum absolute ADC values and those of Definite-NePDHL were compared with contralateral normal white matter (CNWM).

IDH-1 mutational analysis was performed by immunohistochemical staining of all glioblastoma samples in an automated immunostainer using ultraView universal DAB detention kit.

Discriminant analysis was performed between histological diagnosis and presence of Definite-NePDHL. To evaluate prognostic values, we performed Kaplan-Meier survival analysis incorporating the existence of Definite-NePDHL. Multiple regression analysis with Cox proportional hazard model was applied to assess influence of prognostic factors. Log-rank test was performed to assess association between presence of Definite-NePDHL and time-interval of recurrence of tumor.

Results

Definite-NePDHL was present in 25% of glioblastoma patients while it was conspicuously absent in malignant lymphoma and metastatic brain tumors. Specificity and positive predictive values were 100%.

ADC_{MIN} values of malignant lymphomas were higher than those of glioblastomas but were lower compared to metastatic brain tumors. ADC values of Definite-NePDHL were lower compared to those of CNWM.

In glioblastoma subset, higher preoperative Karnofsky performance score ($p=0.0028$), high recursive partitioning analysis class ($p=0.0006$) and total surgical removal ($p=0.0012$) were associated with better median overall survival. Presence of Definite-NePDHL was a significant prognostic factor for decreased survival ($p = 0.0007$) with median overall survival (OS) of 11.9 months. Multivariate analysis with Cox-proportional hazard model showed presence of Definite-NePDHL to be a poor prognostic indicator ($p = 0.0420$).

Cases with D-NePDHL had significantly early local ($p=0.0467$) and distant/dissemination recurrence ($p<0.0001$) and carried poor prognosis ($p=0.0007$). Patients in glioblastoma subset were classified into two groups: Definite-NePDHL positive and Definite-NePDHL negative groups. Logistic regression analysis performed including various determinants showed no statistical difference between these two groups in terms of age, gender, KPS, symptom duration, RPA classification, ADC_{MIN} values and IDH-1 mutational status. Total surgical resection was, however, obtainable in one patient with Definite-NePDHL and in rest 15 cases only non-total resection was obtained ($p = 0.014$).

Discussion

We identified the presence of Definite-NePDHL as an exclusive radiological feature of glioblastoma and utilized the advantage of high-b-value DWI in differentiating

glioblastoma from malignant lymphoma and brain metastases on pre-operative MR-scans. Definite-NePDHL has high specificity in differentiating glioblastoma and carries a poor prognosis.

Although ADC values of glioblastoma, malignant lymphoma and brain metastases are different individual tumors have some overlap. Tumor heterogeneity, difficulty in selecting peritumoral region, infiltration by invading tumor cells and subjective error in selection of ROIs may have resulted in overlapping values. This renders exclusive use of ADC for tumor differentiation unreliable. Definite-NePDHL, on the other hand, is specific enough for definite diagnosis of glioblastoma.

ADC values of Definite-NePDHL were lower compared to CNWM which suggest increased cellularity resulting from infiltration by glioma cells with subsequent cellular compression and decreased free extracellular space. The resulting tumor ischemia due to insufficient vascular proliferation explains why Definite-NePDHL precedes abnormal enhancement and BBB disruption.

D-NePDHL is a significant indicator for early local and distant/dissemination recurrence in glioblastoma. Presence of Definite-NePDHL could also predict the extent of resection obtainable in glioblastoma patients. Total resection was obtainable in one patient with Definite-NePDHL and non-total resection in rest 15 cases. This may be associated with the invasive and/or aggressive character of this tumor sub-group. Study of peritumoral DWI and high b-value DWI is useful for differentiation of glioblastoma.

In conclusion, Definite-NePDHL is a novel diagnostic and specific poor prognostic indicator of glioblastoma and the use of high-b-value DWI is useful for tumor differentiation.