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Original Article

The association between MRI texture analysis and chemoradiotherapy outcomes in glioblastoma cases

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Abstract

Aim: Texture analysis can provide additional information regarding tumor heterogeneity and treatment response. The aim of this study was to evaluate whether MRI texture analysis can predict radiotherapy response and survival in glioblastoma patients.

Material and Methods: A total of 26 patients with pathologically confirmed glioblastoma who had received curative chemoradiotherapy (60 Gy radiotherapy + temozolomide) underwent contrast-enhanced cranial MRI texture analysis before and after chemoradiotherapy. The region of interest was determined as the active tumor area in post-contrast axial T1 sections. The gray level intensity, standard deviation of histogram, entropy, uniformity, skewness, and kurtosis values were determined by texture analysis.

Results: Comparison of the pre- and post-radiotherapy values showed an increase in entropy (6.97±0.37 vs. 7.20±0.30, p = 0.014) and a decrease in uniformity (0.21±0.12 vs.0.16±0.08, p = 0.049). Therefore, radiation therapy was determined to have caused increased heterogeneity in the active tumor region of glioblastoma. The median follow-up was 7.5 [95% confidence interval (1.8-21.63)] months, while the median overall survival was 12.5 [95% confidence interval (4.24-20.81)] months. Young age, high performance statusand low entropy value after radiotherapywere associated with longer survival according to the Kaplan-Meier analysis (p = 0.014, p = 0.031, p = 0.034, respectively).

Conclusion: Based on these results,entropy measurements can be recommended for use as a new prognostic factor for glioblastoma.

Keywords: Glioblastoma; Entropy; Radiotherapy; Survival; Texture Analysis.

INTRODUCTION

Glioblastoma (GBM), a common primary brain tumor, has been reported to have a very poor survival rate (12-15 months) in adults (1,2). Recent studies have shown that maximal resection of GBM followed by radiotherapy with concomitant and adjuvant temozolomide led to increased survival rates (3). The survival after diagnosis also depends on age at diagnosis, tumor location, and histology, Karnofsky performance scores, of surgical resection, duration of neurological symptoms and radiographic response to treatment (4). Magnetic resonance imaging (MRI) is a powerful diagnostic tool that provides high quality images and is often used for the diagnosis of GBM and treatment response. However, the determination of response and progression using anatomic imaging techniques may suffer from issues associated with measurement variability and discordance in interpretation between radiologists (5). Therefore, it is important to develop new imaging tools for better differentiation of treatment-related changes.

There has been increasing interest in the technique of texture analysis over recent years as it has proved to be a significant computer-aided diagnostic tool. Texture analysis evaluates the position and intensity of signals on digital images, thus differentiating using the features of pixels (6). In histogram-based texture analysis, a global statistical evaluation is made of the histogram shape of image intensities in the region of interest (ROI) (7). It is a post-processing technique that enables quantification of a range of parameters including entropy, uniformity, kurtosis, skewness, gray level intensity and standard deviation of the pixel distribution histogram (6). Advances in texture analysis techniques would provide more detailed extracted information of both normal tissue and the tumor compared to the imaging methods in current routine use. A previous study has indicated that accurate radiotherapy target delineation of head and neck cancers could potentially be provided by automated segmentation using texture analysis (8). In addition to reduced uncertainty in target delineation, texture analysis has also

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been examined for treatment response evaluation after radiotherapy (9), early prediction of tumor recurrence after stereotactic ablative radiotherapy (10) and for the prognosis of survival in many types of cancer treated with radiation therapy (11,12).

In studies of brain tumors, MRI texture analysis has been used not only to differentiate different types of brain tumors, such as primary gliomas from metastases, but also for the grading of gliomas (13), and differential diagnosis between radiation necrosis and recurrent brain tumor (14). There have been few studies to date that have examined the effect of MRI texture analysis on survival in GBM patients and its role in predicting response to chemoradiotherapy (CRT) is unknown. Therefore, the aim of this study was to investigate whether MRI texture analysis can predict treatment response and survival in GBM patients treated with CRT.

MATERIAL and METHODS

Chemoradiotherapy

This study enrolled 26 patients with GBM who had completed curative CRT. The study was approved by the Local Clinical Research Ethics Committee. Radiotherapy was delivered to the tumor by linear accelerators (Trilogy, Rapid arc, Varian Medical Systems, Palo Alto, CA) with a nominal energy of 6 MV within a 2-to-3-cm margin of the clinical target volume. Radiation of 2 Gy was given daily 5 days per week (Monday - Friday) for 6 weeks. The total radiation dose was 60 Gy. Quality assurance was performed by means of an individual case review. The concomitant chemotherapy drug, temozolomide, was given daily for as long as the radiotherapy was ongoing (Temozolomide, dose: 75 mg/m^2 daily, 7 days per week until the last day of radiotherapy). Fourweeks after radiotherapy, adjuvant temozolomide was administered for up to 6 cycles, according to the standard 5-day schedule for 28 days. In the first cycle, 150 mg/m^2 of temozolomide was given followed by an increaseto 200 mg/m2 temozolomide at the start of the second cycle. Temozolomide treatment was discontinued if hematologically toxic side-effects were noticed (3). The treatment response to radiotherapy was assessed on MRI taken after one month according to the criteria of the Response Assessment in Neuro-oncology working group (15). These criteria define progression as (a) >25% increase in the size of enhancing lesions at stable or increasing steroid dose, (b) new lesions, (c) increase of lesion size on T2-weighted or FLAIR images, or (d) clinical deterioration. MR spectroscopy was performed when pseudo-progression was suspected. Overall survival (OS) was calculated from the date of the initial diagnosis until death or the last follow-up examination.

Texture Analysis

Contrast-enhanced cranial MRI was taken pre- and post (1-month after) radiotherapy. The MRI examinations were made with a 1.5T GE Optima MR360 device (GE, Milwaukee, USA). The region of interest (ROI) was manually delineated around the tumor to give the largest cross-sectional area on contrast-enhanced axial T1 sections by radiologists (Figure 1). No image filtration was used to quantify the heterogeneity within the ROI. The gray level intensity values of each pixel within the ROI were transferred to MATLAB (MATrixLABoratory, MathworksInc, Natick, USA) version 2009b software. Using first-order statistics such as mean, standard deviation, skewness, and kurtosis, the image gray-level heterogeneity of the pixel intensity distribution was quantified. Skewness measures the asymmetry, and kurtosis the peak of the distribution. Second-order statistics, such as entropy and uniformity, were applied to define the spatial relationship between pairs of pixels.

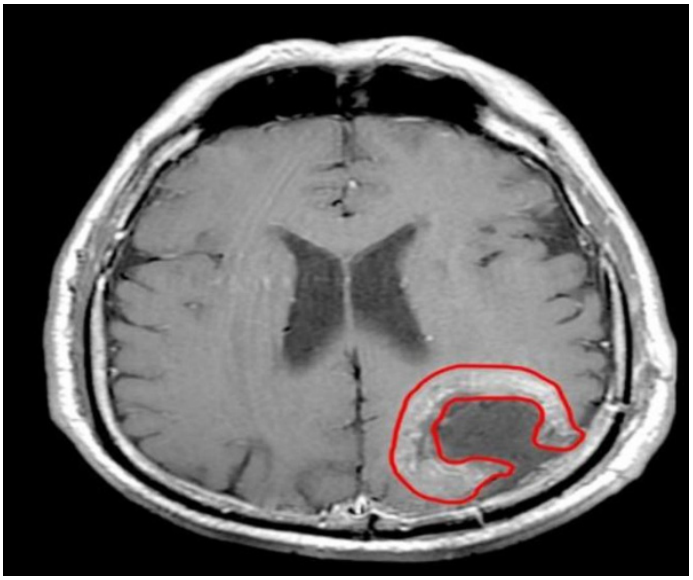

Figure 1. ROI was delineated around the tumor outline for the largest cross-sectional area in contrast-enhanced axial T1 sections

Statistical analyses

All data were analyzed with SPSS 22.0 software (IBM SPSS for Windows version 22, IBM Corporation, Armonk, USA). Radiotherapy-induced changes were calculated using the paired T-test. MRI texture analysis parameters for each patient pre- and post-radiotherapy were dichotomized as lower and higher based on the median values. The correlation between categorical variables was determined using the Chi-square test. The relationship between the groups and survival was calculated using the Log-rank test. The data were analyzed at 95% confidence level and $p < 0.05$ was considered statistically significant.

RESULTS

Evaluation was made of a total of 26 patients, comprising 13 females and 13 males with a median age of 64 years (range, 21-82 years). The comparison of pre- and post-MRI texture analysis showed a significant increase in entropy ($p = 0.014$) and a significant decrease in uniformity ($p = 0.049$) (Table 1). The standard deviation, the gray level intensity and kurtosis increased after radiotherapy but were not statistically significant (Table 1). The skewness decreased after radiotherapy, but did not reach statistical significance (Table 1). These results suggested that the tumor became more heterogeneous after radiotherapy.

The median follow-up was 7.5 (1.8-21.63) months, while the median overall survival was 12.5 (4.24-20.81) months. After radiotherapy, most patients (38.5%, n=10) were in regression and no change was observed in 7patients (26.9%). Disease progression was determined in 9 patients (34.6%). There was no correlation between pre-RTtexture analysis and CRT response (Table 2). The survival rate was associated with low entropy after radiotherapy ($p=0.034$), age<56 years ($p=0.014$) and high Eastern Cooperative Oncology Group (ECOG) performance, ($p = 0.031$) (Figure 2) (Table 3).

Table 1. Changes in texture parameters with chemoradiotherapy

Texture Analysis Parameters	Before RT±SD	After RT±SD	Difference ± SD	95% CI		p
				Lower	Upper	
Gray level intensity	694.68±371.27	714.97±250.11	-20.29±82.43	-190.06	149.47	0.808
Standard deviation	107.39±83.22	141.99±72.79	-34.59±17.11	-69.84	0.64	0.054
Entropy	6.97±0.37	7.20±0.30	-0.22±0.08	-0.40	-0.05	0.014
Skewness	4.25±1.91	3.87±1.79	0.38±0.47	-0.60	1.36	0.435
Kurtosis	0.48±0.81	0.56±0.60	-0.08±0.22	-0.54	0.38	0.723
Uniformity	0.21±0.12	0.16±0.08	0.05±0.02	0.00	0.10	0.049

*Difference between the mean values was calculated by subtracting the mean value after RT from the mean value of pre-RT. RT: Radiotherapy, SD: Standard Deviation, CI: Confidence interval

Table 2. Relationship between chemoradiotherapy response and texture analysis parameters

	Regression n(%)	Stable n(%)	Progression n(%)	p
Gray level intensity	5 (50.0)	2 (28.6)	6 (66.7)	
Low	5 (50.0)	5 (71.4)	3 (33.3)	0.319
High				
Standard deviation	4(40.0)	2(28.6)	7(77.8)	
Low	6(60.0)	5(71.4)	2(22.2)	0.107
High				
Entropy	6(60.0)	3(42.9)	5(55.6)	
Low	4(40.0)	4(57.1)	4(44.4)	0.778
High				
Skewness		5(71.4)	4(44.4)	
Low	4(40.0)	2(28.6)	5(55.6)	0.407
High	6(60.0)			
Kurtosis	5(50.0)	4(57.1)	4(44.4)	
Low	5(50.0)	3(42.9)	5(55.6)	0.881
High				
Uniformity		3(42.9)	5(55.6)	
Low	5(50.0)	4(57.1)	4(44.4)	0.881
High	5(50.0)			

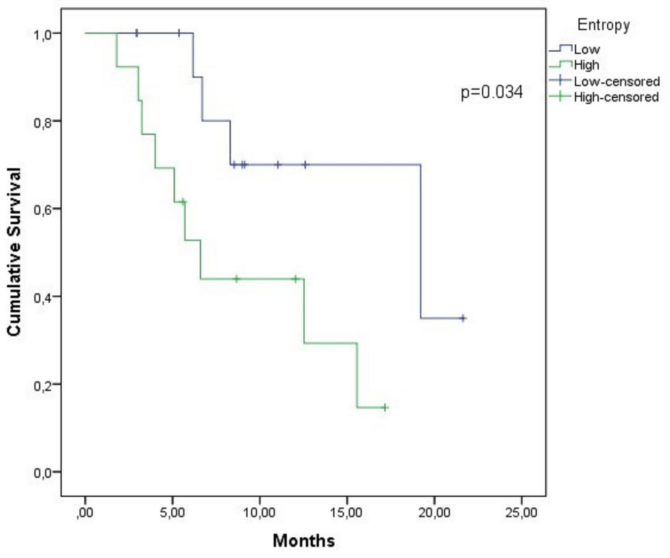

Figure 2. Low entropy after radiotherapy was associated with longer survival according to the Kaplan-Meier analysis

Table 3. Kaplan-Meier analysis results according to the risk factors for overall survival. Texture analysis parameters indicate post-RT values

Characteristic	No. of patients (%)	Overall Survival (months) (95% confidence interval)	p
Age (years)			
≤ 55	9(34.6)	19.2(0.0-39.0)	0.014
> 55	17(65.4)	6.7(4.0-9.2)	
Gender			
Female	13(50)	13.6(1.1-23.8)	0.434
Male	13(50)	10.3(3.5-13.0)	
ECOG performance status			0.031
0&1&2	20(76.9)	15.5(6.9-24.1)	
3&4	6(23.1)	6.6(4.7-8.4)	
Type of surgery			
Biopsy	17(65.6)	8.3(2.0-11.3)	0.060
Subtotal resection	9(37.4)	16.2(13.5-24.8)	
Tumor Localization			
Frontal	8(30.8)	6.7(0.0-14.3)	0.798
Temporal	8(30.8)	15.5(Not available)	
Parietal	10(38.5)	8.3(0.4-16.1)	
Gray level intensity			
Low	13(50)	12.5(6.3-18.7)	0.522
High	13(50)	15.5(0.0-36.2)	
Standard deviation			
Low	13(50)	12.5(4.7-20.3)	0.691
High	13(50)	15.5(5.4-25.6)	
Entropy			
Low	13(50)	19.2(3.4-34.9)	0.034
High	13(50)	6.6(4.2-8.9)	
Skewness			
Low	13(50)	15.5(4.3-26.7)	0.543
High	13(50)	8.3(Notavailable)	
Kurtosis			
Low	13(50)	15.5(3.9-27.1)	0.977
High	13(50)	12.5(4.6-20.4)	
Uniformity			
Low	13(50)	8.3(5.1-11.4)	0.299
High	13(50)	15.5(5.4-25.7)	

DISCUSSION

Tumor heterogeneity is a specific characteristic of malignancy and progression with high cell density, necrosis, hemorrhage, myxoid change (16) and angiogenesis which can cause CRT resistance (17). However, in anatomic imaging techniques, it remains difficult to detect spatial heterogeneity and make associations with measurement variability. Tumor texture may provide additional prognostic information to conventional imaging about tumor heterogeneity. First- and second-order statistics

can be used to measure tumor-derived pixel-based heterogeneity.Previous studies have shown that higher entropy, lower uniformity, higher standard deviation of the pixel distribution histogram, higher kurtosis, and lower skewness led to increased heterogeneity (18). Entropy and difference variance from the edematous region have recently been found to be correlated with hypoxia and could potentially be used on Gd-T1w MR sequences to quantify the structural heterogeneity of GBM tumors, which are highly hypoxic (19).To evaluate the effect of GBM heterogeneity on survival, T1-weighted contrast-enhanced sequences may be used with no necessity for non -contrast T1-weighted, T2-weighted, and FLAIR sequences (20). In the current study, heterogeneity was examined on T1-weighted, contrast-enhanced sequences of the active tumor and histogram-based features were calculated to quantify global heterogeneity in the ROIs of the tumor.

Tumor heterogeneity has been attributed to clonal expansion of multiple tumor populations that are genetically divergent. The drug targets and sensitivities of each clonal population are different. When there are environmental changes, especially chemo- or radiotherapy-induced changes, this variability of importance in allowing minor populations to survive, expand, or become dominant with the previous acquisition of resistant clones (21). The main cause of failure of targeted therapies is due to these clones and tumor relapse after treatment.In addition to structural heterogeneity, MRI texture analysis can also be benefit in characterizing regional genetic heterogeneity, which is of potential diagnostic value with the principle of individualized oncology in GBM (22). In this study, the comparison of pre- and post-MRI texture analysis showed a significant increase in entropy and a significant decrease in uniformity. For the first time in literature, these results suggest that the active tumor area became more heterogeneous after radiotherapy. Based on these findings, it can be assumed that radio-resistant clones survived and radio-sensitive clones were eliminated, thereby increasing intra-tumoral heterogeneity following CRT. Radio-resistant clones causing heterogeneity after treatment caused disease progression and reduced overall survival.

Chaddad et al.examined texture analysis methods in patients with brain tumors prior to treatment, and the brain tumors were classified as 3 phenotypes of active tumor, edema and necrosis (23). The active tumor phenotype predicted overall survival, although entropy did not correlate with survival (23). In the current study, there was also found to be no association between pre-CRT entropy and survival. Lee et al. showed that the homogeneity and entropy of contrast-enhancing lesions of 24 GBM patients were significantly associated with survival. However, they suggested that treatment options such as surgery, radiation, and chemotherapy might have confounding effects on survival rates (24). Interestingly, all the patients in the current study had residual tumor and were treated with curative CRT. Therefore, the current study is important for the determination of survival in GBM groups treated with curative CRT. Based on these results, it can be suggested that post-CRT entropy could be used as a prognostic factor for survival in CRT-treated patients. However, no association was found between CRT response and survival. In accordance with the previous study, it can be said that progression may be exhibited not only by tumor size but also by tumor heterogeneity (25). Therefore, texture analysis could be complementary to radiological response in the clinic, especially when physiological changes precede anatomic changes.

CONCLUSION

In conclusion,the results of this study showed that entropy changed significantly during the course of radiotherapy and was correlated with survival. Based on these findings, entropy measurements one-month post radiotherapy can be recommended for use as a prognostic factor for GBM.

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