Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2017 March 01; 97(3): 586–595. doi:10.1016/j.ijrobp.2016.11.011.

Association of Radiomics and Metabolic Tumor Volumes in Radiation Treatment of Glioblastoma Multiforme

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Abstract

Purpose—To build a framework for investigation of the associations between imaging, clinical target volumes (CTVs), and metabolic tumor volumes (MTVs) features for better understanding of the underlying information in the CTVs and dependencies between these volumes. High-throughput extraction of imaging and metabolomic quantitative features from magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging of glioblastoma multiforme (GBM) results in tens of variables per patient. In radiation therapy of GBM the relevant metabolic tumor volumes (MTVs) are related to aberrant levels of *N*-acetyl aspartate (NAA) and choline (Cho). The corresponding clinical target volumes (CTVs) for radiation therapy are based on contrast-enhanced T1-weighted (CE-T1w) and T2-weighted (T2w)/fluid-attenuated inversion recovery MRI.

Methods and Materials—Necrotic portions, enhancing lesion, and edema were manually contoured on CE-T1w/T2w images for 17 GBM patients. Clinical target volumes and MTVs for NAA (MTV_{NAA}) and Cho (MTV_{Cho}) were constructed. Imaging and metabolic features related to size, shape, and signal intensities of the volumes were extracted. Tumors were also scored categorically for 10 semantic imaging traits by a neuroradiologist. All features were investigated for redundancy. Two-way correlations between imaging and CTVs/MTVs features were visualized as heatmaps. Associations between MTV_{NAA} and MTV_{Cho} and imaging features were studied using Spearman correlation.

Results—Forty-eight imaging features were extracted per patient. Half of the imaging traits were replaced with automatically extracted continuous variables. Twenty features were extracted from

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Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

CTVs and MTVs. A series of semantic imaging traits were replaced with automatically extracted continuous variables. There were multiple (22) significant correlations of imaging measures with CTVs/MTV_{NAA}, whereas there were only 6 with CTVs/MTV_{Cho}.

Conclusions—A framework for investigation of codependencies between MRI and magnetic resonance spectroscopic imaging radiomic features and CTVs/MTVs has been established. The MTV for NAA was found to be closely associated with MRI volumes, whereas very few imaging features were related to MTV_{Cho}, indicating that Cho provides additional information to imaging.

Introduction

It is estimated that 22,850 people in the United States will be diagnosed with primary brain tumors in 2015, of whom 38% will be diagnosed with glioblastoma multiforme (GBM). Glioblastoma multiforme is the most aggressive and rapidly fatal primary brain tumor that occurs in otherwise young and healthy individuals, making this one of the most devastating malignancies in terms of average number of years of life lost (1).

Radiation therapy (RT) combined with temozolamide is the standard clinical treatment for GBM, and magnetic resonance imaging (MRI) is the primary choice for identification of RT treatment volumes (2). Current practice for RT of GBM uses contrast-enhanced T1-weighted (CE-T1w) MRI and fluid-attenuated inversion recovery (FLAIR) and/or T2-weighted (T2w) MRI to define target volumes. Despite using relatively large treatment volumes, in the majority of cases the treatment fails or the cancer reoccurs (3–5). Limitations of MRI to characterize tumor infiltration and tissue viability are believed to impact treatment planning and to contribute to the causes for recurrence. Functional imaging methods, including proton magnetic resonance spectroscopic imaging (MRSI), have been investigated to improve detection of tumor infiltration (6, 7). ¹H spectroscopy can detect and quantify in vivo a number of metabolites, with choline (Cho) and *N*-acetyl aspartate (NAA) being of particular interest for studies of brain tumors (6). Choline is a marker of increased cell membrane proliferation and is increased in tumors. *N*-Acetyl aspartate is related to mature neuronal density and viability and is therefore decreased in tumor tissue where the neuronal cell density is reduced (8–10). In a previous study, volumetric 3-dimensional MRSI was used to construct metabolic tumor volume (MTV) maps of aberrant expression of Cho and NAA (8). When compared with the standard RT clinical target volumes (CTVs), a considerable fraction of MTV_{Cho} was outside of these volumes.

Radiomics is an emerging method for extraction of quantitative imaging features from diagnostic radiographic series (11). Quantification and characterization of these features has been found to reflect tumor molecular characteristics (radiogenomics) and heterogeneity in tumors (12), and specific quantitative MRI parameters have been related to molecular subgroups in GBM (13–16). Recent advances in MRI technology and software make possible the high-throughput extraction of image features of tumors that are outlined (contoured) manually or semi-automatically (11, 14, 15, 17). Features such as lesion size, diameter (long and short), location, areas affected, mass effect, and the presence or absence of contrast enhancement, edema, and necrosis, as well as relative proportions between these volumes, can be seen and quantified on CE-T1w, T2w, and FLAIR MRI.

Increased levels of Cho outside of the MRI-defined brain lesion have been observed and are associated with poor patient outcome (18–20). Similarly, structural MRI radiomic features of tumors have been related to tumor aggressiveness (16). In this study the associations between metabolomic and radiomic features in GBM are investigated. In the process, several established diagnostic MRI features, determined via visual inspection by a neuroradiologist, are successfully replaced with automatically computed continuous values.

Methods and Materials

Patients

From a larger study of 56 treatment-naïve patients with histopathology-confirmed glioma, 20 were grade IV (8, 21). The institutional ethics committee and the research committee Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India approved the study protocol, and informed consent was obtained from the patients or their care providers. In a prior study, 1 patient was removed because of lack of T2w/FLAIR sequence (8); 2 more patients were removed for this work because they did not have CE-T1w imaging. Thus in this report the remaining 17 patients were analyzed. The MRI/MRSI sequences and parameters are included in the Supplementary Materials and Methods (available online at www.redjournal.org) (21). Patient characteristics are summarized in Table E1 (available online at www.redjournal.org). The CE-T1w, T2w MRI, and MRSI data were processed according to previously described methods (21).

Analysis pipeline for radiomics and MTVs

A set of quantitative imaging features for each tumor was obtained for MRSI, CE-T1w, and T2w MRI using MIM Software (MIM, Cleveland, OH). The analysis workflow is shown in Figure E1 (available online at www.redjournal.org). Imaging volumes were manually contoured using the CE-T1w MRI for enhancing and necrotic portions and T2w for edema (Fig. 1A). All image contours were reviewed by a neuroradiologist. Quantitative imaging features, related to size, shape, and signal intensities of the volumes, were extracted. In addition, several categorical image features, described by Diehn et al (15), were recorded by a neuroradiologist. The RT CTVs based on CE-T1w and T2w MRI were constructed (Fig. 1B). Volumetric maps of NAA and Cho distributions were obtained using the Metabolite Imaging and Data Analysis System (MIDAS) package (22) and imported into MIM. The MTVs for these maps were then determined using a comparison with the signal amplitudes in normal-appearing tissue contralateral to the tumor (Fig. 1C) (8). The intersections of CTVs and MTVs were constructed. Similarly to imaging, quantitative features were extracted from the MTVs and CTVs. The association between radiomic and metabolomic features was investigated.

Radiomics dataset

Continuous variables—The volumes of the necrotic (N) core, contrast-enhanced (CE) lesion, and edema (Ed) were extracted and labeled Necrotic volume, CE volume, and Edema volume. In addition, several derivative volumes were defined: Pure CE volume, $V_{PCE} = V_{CE} - V_N$; and Pure Edema volume, $V_{PEd} = V_{Ed} - (V_{CE} \cup V_N)$. Example volumes are shown in Figure 1A. The mean and standard deviation (SD) of the signal intensities were calculated

for CE-T1w and T2w for each of the 5 contours. For image intensities normalization, a volume in the contralateral central white matter (normal-appearing white matter) was also contoured for each patient. The mean and SD of the signal intensities were automatically determined directly from intensities of the pixels within the corresponding contour in MIM and normalized by the mean value in normal-appearing white matter for CE-T1w and T2w. A variable related to the volume shape, or “spiculation,” was calculated by expanding and contracting in 3 dimensions the corresponding volume (Fig. E2; available online at www.redjournal.org). The fraction of the spiculation to the corresponding volume was determined.

In an attempt to standardize the measures and the language used by radiologists, a Visually Accessible Rembrandt Images (VASARI) system was introduced as a reference to categorize and classify GBMs (23). The VASARI MR feature set includes 30 different variables (24). Some of these, related to postoperative features and diffusion, were not applicable to this study. Five imaging features, reported by Diehn et al (15), are part of the VASARI classifications. Here we consider 5 additional VASARI features reported in recent quantitative imaging investigations (17, 25). Gutman et al (17) categorized 3 imaging volumes: CE, Necrosis, and Edema according to the amount present of each volume proportional to the overall tumor (0%–5%, 6%–33%, 34%–67%, 68%–95%, and 95%–100%) that can be directly replaced by continuous variables related to the volumes of CE, Necrosis, and Edema. In addition, the Response Criteria in Solid Tumors (RECIST) is also measured by the longest and shortest diameter of the tumor (26). RECIST was automatically calculated in MIM for each volume and labeled as RECIST *X* long and RECIST *X* short, where *X* = N, CE, or Ed. The MRI analysis yields 39 continuous variables, summarized in Table 1.

Categorical variables—Diehn et al (15) describe associations between 10 image traits and gene expression in GBM tissue samples. The features and their definitions are summarized in Table 2. Each feature is a binary variable (yes or no) based on the association of the patient’s MRI to the categories defined in column 3. The variables are coded as 1 or 2, where 2 corresponds to the worse condition. For instance, if cortical involvement status (yes vs no) is yes, 2 is assigned.

Metabolomics dataset

The metabolomics features are summarized in Table 3. The GBM treatment volumes are defined as previously described (8): (1) CTV receiving 46 Gy, defined as the contrast-enhanced tumor (gross tumor volume [GTV] = CE volume), and the region indicated by the FLAIR/T2 abnormality (Edema = Edema volume) with an additional 2-cm margin (46-Gy volume); and (2) GTV that includes the CE volume with a margin of 2.5 cm and receives a boost to an additional 14 Gy for a total dose of 60 Gy (60-Gy volume). The volumes are exemplified in Figure 1B.

The NAA and Cho metabolic tumor volumes are exemplified in Figure 1C. In addition, several volume measures were investigated: NAA metabolic tumor volume and Cho metabolic tumor volume in relationship to CE volume (the union between Cho volume and

CE volume, the union between NAA volume and CE volume, the percentage of Cho outside of CE volume, the percentage of NAA outside of CE volume). Analogously, metabolic volumes in relationship to Edema volume, 46-Gy volume, and 60-Gy volume were defined (Table 3).

Statistical analysis

The radiomics/metabolomics approach generates hundreds of variables, some of which may be redundant (27, 28). The redundancy in radiomics and metabolomics datasets was examined using Spearman correlation, and features with $\rho > 0.95$ were removed. The autocorrelation matrix was visualized using heatmaps, generated via hierarchical clustering. Statistical calculations and heatmaps were generated in R using the “gplots” package (28).

Spearman correlation coefficients between the radiomics and metabolomics datasets were computed and visualized via 2-way heatmaps, generated using hierarchical clustering on the correlation coefficients. Because there were both continuous and binary variables (nominal or ordinal) in the data and some of the continuous variables did not follow a normal distribution, Spearman correlation was computed instead of point biserial correlation or Pearson correlation. Spearman correlation was also used by Diehn et al (15) to investigate binary (imaging) and continuous (gene expression) variables. Fisher exact test was used to examine the association between 2 categorical variables. Both unadjusted *P* value and adjusted *P* value using the false discovery rate approach for multiple testing adjustment (*q* value) are reported (29). Features with $q < 0.1$ were considered significantly correlated. MATLAB (MathWorks, Natick, MA) was used for the statistical calculations and generating the 2-way heatmap (29–31).

Results

Replacing qualitative imaging features with quantitative imaging values

A neuroradiologist with more than 10 years of experience scored the patients' MRIs according to the definitions of Diehn et al (15) (Table 2). Five of these features could be directly replaced with continuous variables, using the MRI volumes described in Table 1. For example, “absence or presence of necrosis” can be replaced with Necrosis volume; contrast/necrosis ratio – CE Necrosis ratio, etc. The replacement formulas are given in the last column of Table 2. Correlations between imaging traits and continuous variables were significant ($P < .05$) (Fig. E3; available online at www.redjournal.org). The remaining half, indicated in Table 2, were analyzed as categorical variables. Brief definitions for the 5 categorical features and their values for each patient are presented in Table E1 (available online at www.redjournal.org).

Autocorrelation of radiomics features

The total number of analyzed imaging features was 48 (39 from Table 1; 4 continuous and 5 categorical from Table 2). Correlations were calculated between these features and presented as a heatmap in Figure E4 (available online at www.redjournal.org). Two pairs of variables (Pure CE volume and CE volume, CE spiculation volume ratio and Pure CE spiculation volume ratio) had strong correlations ($\rho > 0.95$). Therefore, Pure CE volume and Pure CE

spiculation volume ratio were excluded from subsequent analysis as redundant. The heatmap from the remaining variables (n=46) is shown in Figure 2. The large black square in the upper right corner contains variables, which may be grouped into 2 categories: (1) variables related to the size of necrosis and CE; and (2) variables related to T2w. Further, following the diagonal, there were several clusters, denoted with frames indicating interesting associations between the radiomic features. The next cluster, marked with a black square, contains features related to the edema. Interestingly, the variables related to edema size are also correlated with the features from the top cluster. The next clusters are intensity-related features in CE-T1w and T2w of the imaging volumes. The yellow square cluster in the lower left contains 8 features, 4 that are categorical features for aggressiveness described by Diehn et al (15). Interestingly, this cluster contains the spiculation features, which are also shown to be related to aggressiveness (32). Notably, the features in this “aggressiveness” cluster are inversely correlated with the tumor size (Fig. 2, yellow rectangle in lower left), which is also described in Gevaert et al (33). They are also inversely correlated with (RECIST) length of CE and necrosis, suggesting that as the size of CE increases, the size of the edema decreases (Pure Edema CE ratio), and also as the size of the necrotic portion increases the size of the CE portion decreases (CE Necrosis ratio). Another inverse correlation in the yellow rectangle shows that as size of the necrotic zone and CE increase, the degree of CE decreases.

Autocorrelation of metabolomics features

The heatmap of metabolic/RT volumes' correlations before removal of redundant features is shown in Figure E5 (available online at www.redjournal.org). Eight metabolite variables were redundant ($p > 0.95$): (Cho & 46 Gy volume), (Cho & 60 Gy volume), (Cho & Edema volume), (NAA outside of 46-Gy volume), (NAA & 46-Gy volume), (NAA & 60-Gy volume), (NAA & Edema volume), and (Cho outside of 46-Gy volume). The heatmap of autocorrelation clusters of the remaining variables is shown in Figure 3. Note that besides Cho- and NAA-only clusters, there is a cluster where the variables are mixed.

Correlations between radiomic and metabolic features

The heatmap of 2-way clustering of the correlations between imaging and metabolic/RT features is shown in Figure 4. The color bars on the top of the figure group the imaging features by function (signal intensity, size, and composite/categorical) and location (Edema, CE, Necrotic, or other). A color scale indicating positive correlations in red and negative correlations in blue is seen to the left of the heatmap. The high positive correlations, outlined in blue in the lower left, are the drivers of the clusters with NAA features and based on the green “function” bar on the top are mostly associated with size. Indeed, as previously reported, NAA volume is correlated with the size of the edema (8). However, using the radiomics approach additional associations were found, which underscores the power of the high-throughput approach. In this case, the variables are related to the size of Necrosis (Volume, RECIST long/short). NAA & CE volume has additional positive correlations related to the size of CE (Volume, RECIST long/short). This is expected as GTV encompasses the enhancing lesion and the necrotic core. A cluster containing negative correlations for NAA RT volumes outside of Edema and CE is seen in the blue outline in the upper left. Note that this cluster reinforces the result from the lower cluster in that it is the

metabolic NAA concentration found *outside* of the RT volumes, whereas the previous was for the metabolic NAA *inside* the RT volumes. Indeed, they are negatively correlated with the volumes and size of CE and Necrosis. There is a cluster of negative correlations, outlined in black in the lower right corner, associated with Cho. This cluster, based on the yellow “function” bar, is entirely associated with intensity features. In Table 4 the significant associations between radiomic features and metabolic volumes are presented. Overall there were 40 significant correlations between NAA and radiomic features, a majority of which are related to size (73%). In contrast, there were only 14 significant correlations with Cho ($P=1.73\times 10^{-4}$, Fisher exact test), all related to the intensity and heterogeneity (SD) of the signal on CE-T1w or T2w. After multiple testing adjustment (29), the NAA significant features (n=22, NAA volume [Edema volume, RECIST Edema long/short, Necrosis spiculation], NAA & CE volume [Edema volume, CE volume, Necrosis volume, Pure CE volume, SVZ, RECIST Edema long/short, RECIST CE long/short, RECIST Necrosis long, Necrosis spiculation], %NAA outside of CE volume [CE volume, Pure CE volume, SVZ, Pure Edema CE ratio, RECIST CE long/short], and NAA outside of 60-Gy volume [Necrosis CE-T1w SD]) outnumbered again the Cho significant features (n = 6, Cho volume [Edema T2w SD, CE T2w SD], Cho & CE volume [RECIST Edema short, Edema T2w SD, CE T2w SD], and %Cho outside Edema volume [Edema spiculation]) (q value <0.10).

Discussion

Magnetic resonance imaging is the primary imaging modality for diagnosis and monitoring of GBM and the main imaging modality used for RT planning (34). Metabolic tumor volumes based on aberrant expression of Cho and NAA identify significantly different regions of microscopic infiltration and are being investigated to provide guidance to radiation oncologists for possible areas for treatment (8, 35). The amount of potential information generated by these 3 components, MRI, RT planning, and metabolic imaging, is immense and difficult to interpret without tools for data reduction and visualization. In this exploratory study, a framework for investigation of codependent features found within MRI and RT/metabolic features is presented.

There is an ongoing discussion in the radiomics field of automatic versus radiologist-extracted features (36). The challenge is that although automatically extracted features are more reproducible, they are often impeded by variations in image acquisition and/or artifacts. Semantic features following radiologist evaluation show a high degree of agreement (37) but lack the granularity for satisfactory quantitative analysis. Eight of 13 categorical variables (5 from Diehn et al [15] and 3 from VASARI, Gutman et al [17]) were replaced with continuous variables. A feature for tumor spiculation, associated with tumor aggressiveness, was also added (11). In Gevaert et al (13) a high irregularity of enhancing lesion shape (degree of spiculation) was associated with a lower overall survival rate versus that of a spherical shape (13). An association between edema shape and categorical features indicative of aggressive tumors was found (Fig. 2). To the best of our knowledge, this is the first time such an association has been reported. The image intensity features related to Cho volume (Fig. 4, black box), albeit mostly not significant, suggest that deeper mining of imaging features, such as texture analysis, may yield important associations. The limitation

of the study is that the discovered associations are based on a relatively small number of patients, and further validation in a larger cohort is warranted.

The processing pipeline established in this report enables investigation of associations between imaging and RT/metabolite data. Although some of these correlations were previously described, for example NAA volume and Edema, there are others that need validation using larger datasets. The main result in this report is that Cho shows little associations with MRI-derived radiomic features. This suggests that Cho provides additional information to structural imaging. After the phase 3 randomized, trial, Radiation Therapy Oncology Group 93-05 published their negative results with the addition of a stereotactic radiosurgery (SRS) boost to conventional RT (38), the American Society for Radiation Oncology (ASTRO) released a statement (39), that “one possible flaw with SRS boost techniques is the use of targeting the visible contrast-enhanced lesion. *Magnetic resonance spectroscopy* (MRS) studies have documented areas of increased metabolic activity outside the region of contrast enhancement.” The study did not find evidence that the information contained in Cho can be inferred using just the MRI. Despite the relatively small number of patients, in view of ASTRO recommendations, the present and previous reports (8, 35) provide preliminary data that support the inclusion of MRSI in GBM treatment because: (1) there are aggressive/infiltrative parts of the tumors that are outside of the radiation treatment fields; and (2) the investigated MRI features do not hold promise to predict the distribution of Cho.

In conclusion, a framework for extraction and analysis of quantitative imaging features from MRI, RT volumes, and MRSI was established. The approach will allow for exploration of relationships between sizes, location, and intersection of imaging features of tumors, RT volumes, metabolite concentrations, and comparing those to therapy outcome, quality of life evaluation, and overall survival rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Drs R. K. Gupta and B. Roy for making available the data used for this project.

This publication was supported by grant 10BN03 from Bankhead Coley Cancer Research Program; grants R01EB000822, R01EB016064, and R01CA172210 from the National Institutes of Health; and by Indo-US Science & Technology Forum award 20-2009.

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Summary

A framework for investigation of codependency between high-throughput imaging and metabolomic quantitative features from MRI and MR spectroscopic imaging and radiation treatment volumes of glioblastoma multiforme is established. Series of semantic imaging traits were replaced with automatically extracted continuous variables. Although some of the metabolic volumes were found to be closely associated with MRI features, choline remains elusive for characterization with radiomics, suggesting that choline provides additional information to structural imaging.

Fig. 1.

Description of imaging and metabolic volumes. (A) Contrast-enhanced T1-weighted (CE-T1w) magnetic resonance imaging (MRI) of the brain of a glioblastoma multiforme patient; necrotic and contrast-enhanced areas are identified with red and green arrows, respectively; edema is denoted with a blue arrow in the T2-weighted (T2-w) image (second image lower). Right: Contours of edematous (blue), contrast-enhanced (green), and necrotic (red) tumor tissue types, displayed on CE MRI. Bottom: Contours of evaluated volumes: Necrosis, contrast-enhanced (CE), Pure CE, Edema, and Pure Edema. (B) CE-T1w MRI with clinical target volumes receiving 60 Gy and 46 Gy. (C) Metabolic maps of choline (Cho; top, cyan) and *N*-acetyl aspartate (NAA) (bottom, purple) are obtained from the corresponding 3-dimensional distributions. (A color version of this figure is available at www.redjournal.org.)

Fig. 2. Autocorrelation heatmap depicting hierarchical clustering of Spearman correlation coefficients between radiomics data after removal of 2 redundant features. Intensities indicate high positive (red) and negative (blue) correlations. Interesting correlations, depicted with boxes, are discussed in the text. (A color version of this figure is available at www.redjournal.org.)

Fig. 3. Autocorrelation heatmap depicting hierarchical clustering of Spearman correlation coefficients between metabolomics data after removal of 8 redundant features.

Fig. 4. Heatmap of hierarchical clustering of 2-way correlations between radiomics (columns) and metabolomics (rows) features. The top bars are related to location/function of the radiomics features. Interesting correlations, depicted with boxes, are discussed in the text.

Table 1

Quantitative features

	Feature	Units	Formula
1	Necrosis (N) volume	cm ³	V_N
2	Contrast-enhanced (CE) volume	cm ³	V_{CE}
3	Edema (Ed) volume	cm ³	V_{Ed}
4	Pure CE volume	cm ³	$V_{PCE} = V_{CE} - V_N$
5	Pure edema volume	cm ³	$V_{PEd} = V_{Ed} - (V_{CE} \cup V_N)$
6–8	Spiculation	Volume (cm ³)	S_N, S_{CE}, S_{Ed}
9–13	Spiculation/volume ratio	%	$S_N/V_N, S_{CE}/V_{CE}, S_{CE}/V_{PCE}, S_{Ed}/V_{Ed}, S_{Ed}/V_{PEd}$
14–34	CE-T1w and T2w signal intensity	Mean, standard deviation	$T_{1Mean}, T_{2SD}, T_{2Mean}, T_{2SD} (V_N, V_{CE}, V_{Ed}, V_{PCE}, V_{PEd})$
35–39	RECIST-long and short	cm	$R_{LN}, R_{SN}, R_{LCE}, R_{LEd}, R_{SEd}$

Abbreviations: CE-T1w = contrast-enhanced T1-weighted; T2w = T2-weighted.

Table 2

Categorical features

	Feature	Definition	Formula
1	Infiltrative vs edematous *	Classic “pseudopod” appearance vs diffuse and expansive	
2	Degree of contrast enhancement	5%, >5% of entire tumor volume	$V_{CE}/(V_{Ed} \cup V_N)$
3	Necrosis	Absence or presence of necrosis	V_N
4	Cortical involvement *	CE portion does not extend into cortex	
5	Subventricular zone (SVZ) *	CE portion does not extend into SVZ	
6	Mass effect *	No gross alteration to adjacent structure vs distortion of adjacent structure	
7	Contrast/necrosis ratio	$V_{CE} = V_N$ or $V_{CE} < V_N$	V_{CE}/V_N
8	Contrast/T2w ratio	$V_{CE} < V_{PEd}$ or $V_{CE} = V_{PEd}$	V_{CE}/V_{PEd}
9	Degree of edema	Nonenhancing T2w volume < CE volume, or CE volume	V_{PEd}/V_{CE}
10	T2 heterogeneity *	(>5%, <5%) area of mixed high/low signal in the T2w image of entire tumor volume	

Abbreviations: CE = contrast-enhanced. Other abbreviations as in Table 1.

* Retained for analysis as categorical variables.

Table 3

Metabolic features

	Feature	Definition	Formula
1	GTV	Gross tumor volume from CE-T1w	V_{CE}
2	CTV	Clinical tumor volume, edema from T2w	V_{Ed}
3	CTV_{60}	Clinical tumor volume irradiated with 60 Gy	$V_{CE} + 2.5 \text{ cm}$
4	CTV_{46}	Clinical tumor volume irradiated with 46 Gy	$V_{Ed} + 2 \text{ cm}$
5, 6	MTV_x $x = \text{Cho, NAA}$	Metabolic tumor volume for <i>N</i> -acetyl aspartate (NAA) and choline (Cho)	Cho volume, or NAA volume
7, 8	MTV_x & GTV $x = \text{Cho, NAA}$	Union between metabolic tumor volume and GTV	$MTV_x \cup V_{CE}$ $x = \text{Cho, NAA}$
9, 10	MTV_x out GTV (%) $x = \text{Cho, NAA}$	% of metabolic tumor volume outside of GTV	$[MTV_x - (MTV_x \cap V_{CE})]/MTV_x$ $x = \text{Cho, NAA\%Cho (or \%NAA) outside of CE volume}$
11, 12	MTV_x & CTV $x = \text{Cho, NAA}$	Union between metabolic tumor volume and CTV	$MTV_x \cup V_{Ed}$ $x = \text{Cho, NAA\%Cho (or \%NAA) and Edema volume}$
13, 14	MTV_x out CTV (%) $x = \text{Cho, NAA}$	% of metabolic tumor volume outside of CTV	$[MTV_x - (MTV_x \cap V_{Ed})]/MTV_x$ $x = \text{Cho, NAA\%Cho (or \%NAA) outside of Edema volume}$
15, 16	MTV_x out CTV_y $x = \text{Cho, NAA}$ $y = 46, 60 \text{ Gy}$	Metabolic tumor volume outside of CTV	$[MTV_x - (MTV_x \cap CTV_y)]/MTV_x$ $x = \text{Cho, NAA}$ $y = 46, 60 \text{ Gy Cho (or NAA) outside of 46-Gy (or 60-Gy) volume}$
17–20	MTV_x & CTV_y $x = \text{Cho, NAA}$ $y = 46, 60 \text{ Gy}$	Union between metabolic tumor volume and clinical target volume	$MTV_x \cup CTV_y$ $x = \text{Cho, NAA}$ $y = 46, 60 \text{ Gy Cho (or NAA) and 46-Gy (or 60-Gy) volume}$

Abbreviations as in Tables 1 and 2.

Table 4

Significant correlation coefficients between radiomics and metabolomics features

A	NAA volume																				Cho volume				B
	Edema volume	Pure Edema volume	T2 het	RECIST Edema long	RECIST Edema	Necrosis spiculation															RECIST CE long	Edema T2w SD	CE T2w SD		
p	0.770	0.569	0.559	0.647	0.669	0.623															0.216	-0.752	-0.333		
CI	(0.459 0.913)	(0.121 0.824)	(0.107 0.809)	(0.242 0.860)	(0.278 0.870)	(0.202 0.849)															(-0.296 0.631)	(-0.906 0.426)	(-0.844 0.183)		
q	0.003	0.172	0.159	0.028	0.033	0.038															0.439	0.005	0.093		
p (raw)	0.000	0.017	0.020	0.005	0.003	0.008															0.406	0.000	0.009		
NAA & CE volume																					Cho & CE volume				
	Edema volume	CE volume	Necrosis volume	Pure CE volume	SVZ	T2 het	RECIST Edema long	RECIST Edema	RECIST CE long	RECIST CE short	RECIST Necrosis	RECIST Necrosis	CE spiculation	Necrosis spiculation	Pure CE T1	RECIST Edema	Edema T1 SD	Edema T2w SD	Pure Edema	CE T2w					
p	0.689	0.885	0.728	0.885	0.559	0.522	0.641	0.605	0.691	0.787	0.647	0.559	0.583	0.804	0.483	0.549	-0.566	-0.627	-0.522	-0.561					
CI	(0.311 0.879)	(0.703 0.958)	(0.380 0.895)	(0.703 0.958)	(0.107 0.819)	(0.055 0.801)	(0.232 0.858)	(0.176 0.841)	(0.315 0.880)	(0.492 0.920)	(0.242 0.860)	(0.107 0.819)	(0.143 0.831)	(0.527 0.927)	(0.003 0.782)	(0.093 0.815)	(-0.823 0.118)	(-0.851 0.210)	(-0.802 0.055)	(-0.821 0.110)					
q	0.011	0.000	0.009	0.000	0.098	0.159	0.028	0.050	0.021	0.002	0.050	0.197	0.140	0.001	0.496	0.075	0.178	0.035	0.158	0.095					
p (raw)	0.002	0.000	0.001	0.000	0.020	0.032	0.006	0.010	0.002	0.000	0.005	0.020	0.014	0.000	0.050	0.022	0.018	0.007	0.032	0.019					
%NAA outside of CE volume																%Cho outside of CE volume									
	CE volume	Necrosis volume	Pure CE volume	Degree CE	SVZ	CE Pure Edema	Pure Edema CE ratio	RECIST CE long	RECIST CE short	RECIST Necrosis	Pure Edema T1					CE spiculation	Necrosis CE-T1w								
p	-0.654	-0.551	-0.569	0.534	-0.559	-0.569	0.625	-0.635	-0.654	-0.485	-0.485					-0.495	0.507								
CI	(-0.863 0.253)	(-0.816 0.096)	(-0.824 0.121)	(0.072 0.808)	(-0.819 0.107)	(-0.824 0.121)	(0.206 0.850)	(-0.855 0.222)	(-0.863 0.253)	(-0.783 0.006)	(-0.783 0.006)					(-0.788 0.019)	(0.035 0.794)								
q	0.022	0.109	0.086	0.271	0.098	0.172	0.073	0.031	0.022	0.242	0.483					0.217	0.188								
p (raw)	0.004	0.022	0.017	0.027	0.020	0.017	0.007	0.006	0.004	0.048	0.048					0.043	0.038								
%NAA outside of Edema volume												%Cho outside Edema volume													
	SVZ	CE spiculation	Pure CE spiculation	Pure Edema T2 SD	Pure CE T2 SD																	Edema spiculation	CE-T1w Mean	CE T2w Mean	Pure CE T2w
p	-0.484	0.515	0.554	-0.525	-0.578																	-0.615	-0.529	0.542	0.542
CI	(-0.783 0.005)	(0.045 0.796)	(0.100 0.817)	(-0.803 0.059)	(-0.625 0.135)																	(-0.846 0.191)	(-0.805 0.065)	(0.082 0.811)	(0.082 0.811)
q	0.162	0.257	0.210	0.158	0.150																	0.086	0.289	0.247	0.139
p (raw)	0.049	0.035	0.021	0.031	0.015																	0.009	0.029	0.025	0.025
NAA outside of 60 Gy volume																					Cho outside 60 Gy volume				
	Edema spiculation	Necrosis CE-T1w SD	RECIST CE short																						
p	0.542	0.652	-0.494																						
CI	(0.084 0.812)	(0.249 0.862)	(-0.787 0.017)																						
q	0.245	0.046	0.147																						
p (raw)	0.024	0.005	0.044																						
				Pure CE T2w Mean																					
				0.532																					
				(0.069 0.807)																					
				0.139																					
				0.028																					

Abbreviations as in Tables 1 and 2.

Significant correlation coefficients between radiomics and metabolomics features at 95% confidence interval including the adjusted P value q , and raw P value for (A) NAA, and (B) Cho. There were 40 significant correlated features for NAA and 14 for Cho ($p > |0.48|$), $P = 1.73 \times 10^{-4}$, Fisher test. Significant features ($q < 0.1$) after multiple testing adjustment are highlighted. (outlines for the highlighted boxes are not showing up)