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Title

Multi-parametric MR Imaging Biomarkers Associated to Clinical Outcomes in Gliomas: A Systematic Review

Running title

Review of multi-parametric MRI biomarkers in Gliomas

Title Page

Multi-parametric MR Imaging Biomarkers Associated to Clinical Outcomes in Gliomas: A Systematic Review

Systematic Review

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Structured Abstract

Purpose - To systematically review evidence regarding the association of multi-parametric biomarkers with clinical outcomes and their capacity to explain relevant subcompartments of gliomas.

Materials and Methods - Scopus database was searched for original journal papers from January 1st, 2007 to February 20th, 2017 according to PRISMA. Four hundred forty-nine abstracts of papers were reviewed and scored independently by two out of six authors. Based on those papers we analyzed associations between biomarkers, subcompartments within the tumor lesion, and clinical outcomes. From all the articles analyzed, the twenty-seven papers with the highest scores were highlighted to represent the evidence about MR imaging biomarkers associated with clinical outcomes. Similarly, eighteen studies defining subcompartments within the tumor region were also highlighted to represent the evidence of MR imaging biomarkers. Their reports were critically appraised according to the QUADAS-2 criteria.

Results – It has been demonstrated that multi-parametric biomarkers are prepared for surrogating diagnosis, grading, segmentation, overall survival, progression-free survival, recurrence, molecular profiling and response to treatment in gliomas. Quantifications and radiomics features obtained from morphological exams (T1, T2, FLAIR, T1c), PWI (including DSC and DCE), diffusion (DWI, DTI) and chemical shift imaging (CSI) are the preferred MR biomarkers associated to clinical outcomes. Subcompartments relative to the peritumoral region, invasion, infiltration, proliferation, mass effect and pseudo flush, relapse compartments, gross tumor volumes, and high-risk regions have been defined to characterize the heterogeneity. For the majority of pairwise co-occurrences, we found no evidence to assert that observed co-occurrences were significantly different from their expected co-occurrences (Binomial test with False Discovery Rate correction, α=0.05). The co-occurrence among terms in the studied papers was found to be driven by their individual prevalence and trends in the literature.

Conclusion - Combinations of MR imaging biomarkers from morphological, PWI, DWI and CSI exams have demonstrated their capability to predict clinical outcomes in different management moments of gliomas. Whereas morphologic-derived compartments have been mostly studied during the last ten years, new multi-parametric MRI approaches have also been proposed to discover specific subcompartments of the tumors. MR biomarkers from those subcompartments show the local behavior within the heterogeneous tumor and may quantify the prognosis and response to treatment of gliomas.

Keywords

- Biomarkers, Tumor
- Patient Outcome Assessment
- Magnetic Resonance Imaging
- Magnetic Resonance Spectroscopy
- Image Processing, Computer-Assisted
- Glioma, Subependymal

Multi-parametric MR Imaging Biomarkers Associated to Clinical Outcomes in Gliomas: A Systematic Review

Systematic Review

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Conclusion - Combinations of MR imaging biomarkers from morphological, PWI, DWI and CSI exams have demonstrated their capability to predict clinical outcomes in different management moments of gliomas. Whereas morphologic-derived compartments have been mostly studied during the last ten years, new multi-parametric MRI approaches have also been proposed to discover specific subcompartments of the tumors. MR biomarkers from those subcompartments show the local behavior within the heterogeneous tumor and may quantify the prognosis and response to treatment of gliomas.

1. Introduction

Gliomas are tumors that arise from glial cells. Types of glioma include astrocytoma, oligodendroglioma, and a number of diagnostic categories classified as other gliomas and mixed neuronal-glial tumors. A grade of malignancy, ranging from I to IV, is assigned to each specific tumor class; grade I and II tumors are known as low-grade gliomas, while grade III and IV tumors are considered high-grade gliomas [1]. According to the report in the United States from 2008 to 2012 [2], gliomas represent approximately 27% of all central nervous system (CNS) tumors in adults and 53% of CNS tumors in children and adolescents aged 0-14 years in the United States. Most importantly, 80% of malignant tumors are gliomas. In particular, glioblastoma, a high-grade glioma with predominantly astrocytic differentiation, accounts for the majority of gliomas (55%) and 46% of all malignant CNS tumors and carries the worst prognosis.

Gliomas and especially high-grade gliomas are heterogeneous masses at phenotypic, physiologic, and genomic levels [3,4,5]. Such condition implies difficulties in standard of care definitions. Multiple research studies have tackled this heterogeneity attempting to define biomarkers relative to clinical outcomes by delineating regions of interest in the tumors.

MR imaging biomarkers are biological features extracted from MR imaging able to support decisions during the management of patients. Multi-parametric image biomarkers are compositions of complementary image biomarkers willing to represent the patients' conditions better than single biomarkers. Tumor subcompartments are areas of differing underlying biology within the heterogeneous tumor region where image biomarkers could provide clinically relevant information.

This paper reports a literature systematic review of evidence regarding the definition of multi-parametric MR imaging-based biomarkers associated with clinical outcomes and their capacity to explain relevant subcompartments in patients with glioma. We sought to address two main clinical questions in this population: (1) which multi-parametric MR imaging biomarkers can be associated with clinical outcomes? and (2) which subcompartments have been defined in multi-parametric MR images? For each question, we will analyze the journal papers published in a period of 10 years that used multi-parametric MR image biomarkers to study clinical outcomes and patient conditions. We gave special attention to those ~~journals including~~ papers presenting the definition of subcompartments within the tumor lesion based on multiple MR images and their relation with clinical outcomes.

2. Materials and Methods

2.1 *Evidence acquisition*

This systematic review was performed after collecting published scientific documents until February 20th, 2017, reporting original studies where multi-parametric MR biomarkers were related to clinical outcomes and/or patient conditions. The identification of documents was mainly achieved using the Scopus advanced search engine to query the Scopus citation database (1083 papers). The general terms of the query were *magnetic resonance, glioma, multi-parametric MR biomarker* and *subcompartment*. These terms were instantiated in specific terms building a Scopus advanced query that was executed on February 20th, 2017 (see Table S1a in Supplementary material for details). A query to PubMed database through its "PubMed Advanced Search Builder" and its thesaurus called *MeSH* (Medical Subject Headings) added 83 references to the list of identified papers of the study.

Focusing on the query logic, at the initial point we started with the following selection criteria: all papers that contain the term "magnetic resonance imaging" (accepting also "mr", "mri" or "perfusion") together with the word "glioma or glioblastoma" in its title, abstract or keywords. Then, we were adding more conditions aiming to adjust as much as possible the obtained results. Going deeply into the query executed (showed in Table S1a), it can be divided into 5 different sub-queries (broken down in Table S1b of the Supplementary File), following these patterns:

1. Studies of multiparametric MRI and/or subcompartments in gliomas
2. Studies of MRI for predicting clinical outcomes or conditions in patients with glioma
3. Studies of vascularity MRI in gliomas
4. Studies of MRI and molecular profiling in gliomas
5. Studies of contrast-enhanced MRI biomarkers in gliomas

We specified exclusion criteria for those papers classified as reviews in the Scopus database (using the field "doctype"). Lastly, there were considered only articles written in English language.

After filtering from 1st, 2007 to February 20th, 2017 and eliminating duplicates we screened 815 records by reviewing titles. In the next step, we excluded 166 papers by consensus between authors JGG and MOS after reviewing carefully their titles; the main reason was the lack of using magnetic resonance imaging techniques, but there were others like using other techniques (CT, SPECT, etc.), some case reports and others were out of our scope. Then we cope with 649 abstracts and all of them were reviewed by JGG and

MOS, discarding 200 because they did not associate multiple biomarkers to clinical outcomes or patient conditions.
At that moment, we decided to make an extensive review of all the selected abstracts in order to extract the maximum information that we consider important for our study. Thus, two out of six authors (from JGG, MOS, EFG, JJA, APG and RSR) evaluated the selected 449 studies by a set of features relative to: the population, research design (retrospective vs. prospective study; transversal vs. longitudinal study and evaluation criteria), diagnosis, clinical outcome, treatment, management time point at the MR exam, MR field strength, MR sequence, analysis techniques, MR biomarkers and tumor subcompartments. The catalog of values for each feature was prospectively defined from the keywords used in the abstracts of the papers. The valuable and detailed information collected at this point has been the basis of this review.
Table1 summarizes the variables extracted from the 449 abstracts included in the qualitative synthesis. The table shows for each feature the number of abstracts with information and the categorized values list. For clarity, only the most frequent values for the variables are included in the table. For a complete list of variables, readers may visit the supplementary material. The file that contains the characterized data for all the abstracts selected is publicly available in the Supplementary File (*statsQueries_MultiparametricMRI.xlsx*).

Table1. Table1_featuresExtracted

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) process for reporting included and excluded studies was adhered to. The flow diagram of the process is shown in Fig 1.

Fig 1. Fig1_flowchart

2.2 *Assessment of study quality*

We evaluated in more detail the final set of 45 highlighted papers for the considered questions by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [6]. The overall quality of the studies was fair to good, with low risk of bias and concerns about applicability (Fig. 2). Table S5 of Supplementary File provides the detailed analysis of risk of bias and applicability concerns.

Fig 2. Fig2_quadas2

2.3 *Qualitative synthesis*

During the review, the authors scored every abstract in a 0 to 10 scale given the relevance of the previously defined features for our clinical questions. The 45 papers with scores equal or higher than 8 were highlighted. From them, 18 defined tumor subcompartments and the other 27 did not. We analyzed the quality of our study using QUADAS-2 criteria over the highlighted papers, as mentioned in the previous section “assessment of study quality”.
In the procedure to assign a score to a paper, the main variables taking into consideration have been: clinical outcomes, MR biomarkers, and subcompartments. These three features have had the biggest weight of the score, but the others have also been important to get the final value. For example, if one study has a population of 5 patients and another similar study carries out 50 patients, the later get a better score. In short, the score has to be understood as a measure of the relevance of every paper related to the clinical question to be answered.
After reviewing the 449 abstracts, the distribution of papers assigned to every score is presented in Table2:

Table2. Table2_scoresDistribution

3. Results

3.1 *Populations studied*

Most of the papers (317 out of 449, 70%) assessed in the review were targeted to adults and the median (± mean absolute deviation) number of individuals in their studies was 37±17. Additionally, it is worth to mention the high number of studies addressing glioblastoma (169 out of 449, 38%) and, more generally, high-grade gliomas (278 out of 449, 62%). Most study designs were transversal (366 out of 449, 82%) and retrospective (371 out of 449, 83%). Table S2 in Supplementary File gives a complete number of the target populations, a number of individuals, diagnoses and study designs of assessed studies.

3.2 *MRI studies*

Most of the procedures were carried out before the surgical intervention (199 out of 449, 44%). The second most studied time point was at follow-up (51 out of 449 articles, 11%). Finally, only 25 studies were carried out during recurrence (6%). In total, there were 142 studies performed after surgery (32%).

Most papers did not report the used MR field strength in the abstract. There was a high variability in the type of MR sequences included in the studies. Most studies focused on functional images, including perfusion (PW) (174 studies, 39%) and diffusion-weighted (DW) images (117 studies, 26%). Standard morphologic MR images were also routinely used (182 out of 449, 41%). See Table S3 in Supplementary File for details.

3.3 *Clinical outcomes and treatments*

Most papers defined overall survival (OS) as the main response variable of the study (177 out of 449, 39%). Fewer studies were able to study progression-free survival (PFS) (41 studies, 9%), time to progression (TTP) (3 studies, <1%), recurrence (33 studies, 7%), tumor progression (12 studies, 3%) and RANO criteria (2 studies, <1%). Some studies also included molecular profiling and biological functions as response variables (51 out of 449, 11%). As expected, diagnosis and grading were clinical outcomes highly evaluated, appearing each one in 104 papers (23% each one).

Most of the studies did not directly refer to a specific treatment. This was in part due to the high number of preoperative studies. Nevertheless, it is likely that most postoperative patients received the standard treatment based on radiation therapy and Temozolomide [7]. Bevacizumab (with 25 studies) and Temozolomide (with 15 studies) were the most cited specific treatments. Table S4 in Supplementary File shows the clinical outcomes and treatments of the studies assessed in this review.

3.4 *Which multi-parametric MR imaging biomarkers can be associated with clinical outcomes?*

Imaging biomarkers were classified into two groups: biomarkers based on feature extraction methods and biomarkers for specific MR-sequences. Biomarkers based on feature extraction methods are independent of the MR sequence and are related to volumes, areas, texture features, shapes and image moments from morphologic or functional images (3rd to 11th rows of Table S6 in Supplementary File). Besides, biomarkers for specific MR sequences were extensively used in the reviewed literature and includes the quantification of Cerebral Blood Volume (CBV) (112 studies), K_{trans} (31 studies) and ADC (79 studies), among others. Moreover, authors defined specific biomarkers based on metabolite concentration or ratios extracted from Chemical Shift Imaging (CSI). Table S6 summarizes the MR imaging biomarkers used in the studies selected for this review.

Figure 3 summarizes the relationships found among MR imaging biomarkers and the most prevalent clinical outcomes. In this graphical network, the thickness of the edges is linearly relative to the number of papers where the concepts appear connected; these connections have been calculated from the co-occurrence matrix between all pairs of terms showed in the graph, using R routines [64].

Fig 3. Fig3_ subrogatedbiomarkers

In that context, there were observed some strong co-occurrences between biomarkers and clinical outcomes as well as biomarkers with each other. Specifically, CBV biomarker was used several times in combination with ADC (26 papers, 5.7%) and spectroscopic metabolites, such as choline (Cho) and creatine (Cr) (20 and 18 papers, respectively). These co-occurrences were not significantly different from their expected co-occurrences given by their individual prevalence (Binomial test with False Discovery Rate correction, α=0.05). Nevertheless, this high prevalence may reflect the search for complementary information provided by the biomarkers. Whereas CBV indicates vascularization of tumor region [8], ADC is a biomarker grading cellular density and integrity, and therefore related to tumor growth and necrosis [9]. Moreover, metabolites are the functional fingerprint of protein functions, genetic variations and environmental effects [10].

In view of the results, overall survival and PFS were evaluated mainly by perfusion biomarkers, such as CBV (OS-CBV in 17 papers, 3.7%; PFS-CBV in 11 papers, 2.4%). ADC was also used for survival analysis (OS-ADC in 8 papers, 1.7%), while there were fewer studies of survival based on the MR spectroscopic analysis of tumor metabolites. Progression-free survival was mainly analyzed by ADC, CBV, N-acetyl-aspartate (NAA), Glutamate (Glu), Glutamine (Gln) and Myo-inositol (mI). Moreover, the association of molecular profiling with perfusion biomarkers was largely studied by the reviewed papers. Additionally, the association of mI, NAA, Cho, lactate, and lipids with molecular profiling was extensively studied as well.

Table 3. Table3_biomarkers

Twenty-seven highlighted journal papers were included in Table 3 [11-37]. All clinical outcomes were studied, at least once, by the combination of three or more types of MR exams. Twelve papers associated MR biomarkers to progression, recurrence or survival. From them, 9 extracted morphologic biomarkers, 7 used perfusion coefficients, 5 used diffusion parameters and 4 quantified different MRS/CSI metabolites. Apart from that, morphologic images and perfusion coefficients were used in 3 studies of molecular profiling, whereas ADC was used in 2 and MRS/CSI in 1, respectively. Morphologic features were used in 5 out of the 6 studies for tumor grading to discriminate gliomas after manual segmentation, whereas MRS/CSI was also used in 4 of them. Moreover, only 2 studies performed segmentations as a primary goal of the multi-parametric study: the first one combined morphologic images (T1, T2, FLAIR and T1c), while the second one combined them with PW and DW imaging studies. Only O'Neill et al. [19] studied response to treatment (VEGF Trap) using morphologic images, DCE, DWI, and FDG-PET. Besides, only Durst et al. [36] estimated nuclear density to predict tumor infiltration in a study from morphologic, perfusion and diffusion images. It is also relevant to highlight that radiomics and radiogenomics techniques were applied during the last years to define relevant biomarkers from MR images in gliomas.

3.5 *Which subcompartments have been defined in multi-parametric MR images?*

Morphologic regions (such as tumor, edema, and necrosis), broad volumes of interest, intensity-based regions (enhanced tumor, non-enhanced tumor) or regions from functional images (such as contrast-enhanced tumor or hypoperfused tumor volume) guided the majority of the studies. Several studies defined morphological subcompartments of the tumor, such as the center of the tumor (8 studies), the rim of the tumor (3 studies) or the peritumoral region (17 studies). Others focused on treatment-response compartments, such as radiation-induced edema (1 study) and resection cavities (3 studies). Different conditions of the local regions (e.g. specifically hypoxia and mass effect) and biological processes associated with cancer, such as infiltration and vascular disruption, defined functional regions of the tumors. Less specific but still focused on defining subcompartments were those studies showing heterogeneous lesions in contrast to homogeneous lesions. As expected, specific locations of the tumor were also studied: locations involving basal ganglia, corpus callosum, caudate putamen or close to the cerebrospinal fluid. Table S7 in Supplementary File includes all references to subcompartments and regions defined in the reviewed papers. Additionally, Table S8 in Supplementary File lists the analysis techniques and statistical tests performed by the studies included in this review.

Figure 4 shows the graphical network of the relationships among subcompartments, MR imaging biomarkers and clinical outcomes. Although the most prevalent regions in the eligible studies are relative to the morphology of the tumor, several studies defined specific regions associated with response to treatment and the tumor characterization at different levels. It is important to mention that the obtained co-occurrences were not significantly different from their expected.

Fig 4. Fig4_subcompartments

The question "which subcompartments have been defined in multi-parametric MR images?" is answered in S2 Table [38-55]. Whereas typical morphologic-derived compartments, such as enhancing tumor, edema and necrosis have been studied during the last decades, more specific subcompartments or regions have been defined only in multi-parametric studies. The peritumoral region has been widely studied with different morphologic, perfusion, diffusion and metabolic biomarkers for either diagnosis, grading or survival analysis. Moreover, specific compartments such as relapse compartments, gross tumor volumes, high-risk volumes, and non-specific clustering compartments have been defined for overall survival, progression-free survival and recurrence. Besides, Christoforidis et al. [54] defined tumoral pseudoblush as a marker for increased tumoral microvascularity. Finally, the study to connect the subcompartments with high levels of invasion, infiltration, proliferation, mass effect and FLAIR hyperintensity with different molecular profiles of gliomas was of special interest to this review.

Table 4. Table4_subcompartments

4. Discussion

Multiple image biomarkers have demonstrated their association to clinical outcomes of glioma, including diagnosis, grading, segmentation, overall survival, progression-free survival, recurrence, molecular profiling and response to treatment. Combinations of biomarkers, such as PW, DW, and CSI, with radiomics features from morphological exams (T1, T2, FLAIR, and T1c) are the preferred MR biomarkers in the state of the art.

There is a trend to delineate subcompartments, relative to tumor progression and specific biological processes in gliomas. As it is said in Hanahan [56], the biology of a tumor can only be understood by studying the individual specialized cell types within it, and taking into consideration the "tumor microenvironments" that the cells construct during the course of multistep tumorigenesis. In addition to the characterization of the peritumoral region, relapse compartments, gross tumor volumes, high-risk volumes,

and non-specific clustering compartments have been defined for overall survival, progression-free survival and recurrence. Besides, subcompartments within gliomas with high invasion, infiltration, proliferation, mass effect and pseudoflush are markers of differential molecular profiles and tissue characterization.
Potential clinical benefits of incorporating MR imaging biomarkers and delimiting accurately the different subcompartments to the clinical practice include advancements in surgery and radiotherapy planning, adjuvant treatment selection, assessment of response, early recurrence detection and selection of subsequent therapies. Moreover, this integrated approach will contribute to a better characterization of glioma subgroups, identification of new circulating biomarkers, and identification of new targets for the treatment of patients with glioma.
The definition of accurate multi-parametric MR biomarkers for specific tumor regions may help on the interpretation of treatment response in early stages, allowing active planning during multidisciplinary treatments. Macdonald's [57] and RANO criteria [58] based on bi-dimensional measurements and WHO standards for reporting results of cancer treatment may not reflect non-enhancing patterns of infiltration, neither the effect of specific therapies (such as anti-angiogenic therapies on high-grade gliomas) [59]. Moreover, manual procedures to delineate complex patterns are not plausible. Despite improvements made by the RANO criteria, the delineation of subcompartments based on multi-parametric MR biomarkers to routine practice may achieve a more accurate characterization of tumors and could be very helpful in the difficult task of depicting the tumor heterogeneity.
With the objective to achieve a more reliable characterization of brain tumor biology at the molecular level, MRI can be combined with another diagnostic technique called positron emission tomography (PET). PET can provide this detailed metabolic information, which when combined with the high spatial and contrast resolution of MRI could help tailor treatment regimens at an early stage [60].
By using radioactive tracers, PET can provide quantitative information of cellular activity and metabolism of the tumor tissue. Amino acid PET tracers are recommended as a complement to MRI by current guidelines in brain tumor imaging. This have proven promising for defining true tumor volume and differentiating viable tumor tissue from postoperative changes or radiation necrosis, and as a guide to select the best biopsy sites in gliomas.
Hybrid PET/MRI have the potential to improve the diagnostic accuracy compared to MRI alone. Castiglioni [61] describes that hybrid PET/MRI represents an innovative diagnostic technology for non-invasive in vivo imaging of cancer; the preliminary results are showing potentials to enter the technique in the clinical setting. It also represents a reduction of radiation exposure which implies benefits for patients.
PET/MRI tomographs open new perspectives for clinical and research applications and attract a large interest among the medical community. This new hybrid modality is expected to play a pivotal role in a number of clinical applications [62]. Finally, as Marner [63] stress in their article, there are still a number of caveats in using a PET/MRI scanner, but solutions to overcome the challenges are being developed.
It is important to note that most reviewed papers did not provide molecular profiling (i.e., IDH mutation and 1p/19q codeletion status) to use the 2016 World Health Organization classification of tumors of the CNS (WHO CNS) [1].

5. Conclusion

Combinations of MR imaging biomarkers from morphological, PWI, DWI and CSI exams have demonstrated their capability to predict clinical outcomes in different management moments of gliomas. Whereas morphologic-derived compartments have been mostly studied during the last ten years, new multi-parametric MRI approaches have also been proposed to discover specific subcompartments of the tumors. MR biomarkers from those subcompartments show the local behavior within the heterogeneous tumor and may quantify the prognosis and response to treatment of gliomas.
The understanding of the underlying behavior of the different tumor tissues in terms of their distribution and topology along the lesion and the specific properties of sub-regions is mandatory to improve therapy planning. The possibility to know which parts of the homogeneous tumor are more aggressive may provide critical information to improve the survival of the patients.

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Figure legends

Fig 1. Flow diagram for systematic reviews and meta-analysis (PRISMA) showing the outcome of the initial and additional searches resulting in the full studies included in the review.

Fig 2. Results for risk of bias and concerns about applicability using the QUADAS-2 criteria.

Fig 3. Graphical network with the relationships among MR imaging biomarkers and clinical outcomes. The thickness of the edges is linearly related to the number of papers where the concepts appear connected.

Fig 4. Graphical network with the relationships among subcompartments, MR imaging biomarkers, and clinical outcomes. The thickness of the edges is linearly related to the number of papers where the concepts appear connected.

Table legends

Table 1. Data extracted from the 449 abstracts selected for qualitative synthesis.

Table 2. Number of papers per each score after the author's revision.

Table 3. Selected papers that use multi-parametric MR imaging biomarkers to predict clinical outcomes in gliomas.

Table 4. Selected papers that define subcompartments and multi-parametric MR imaging biomarkers to predict clinical outcomes in gliomas.

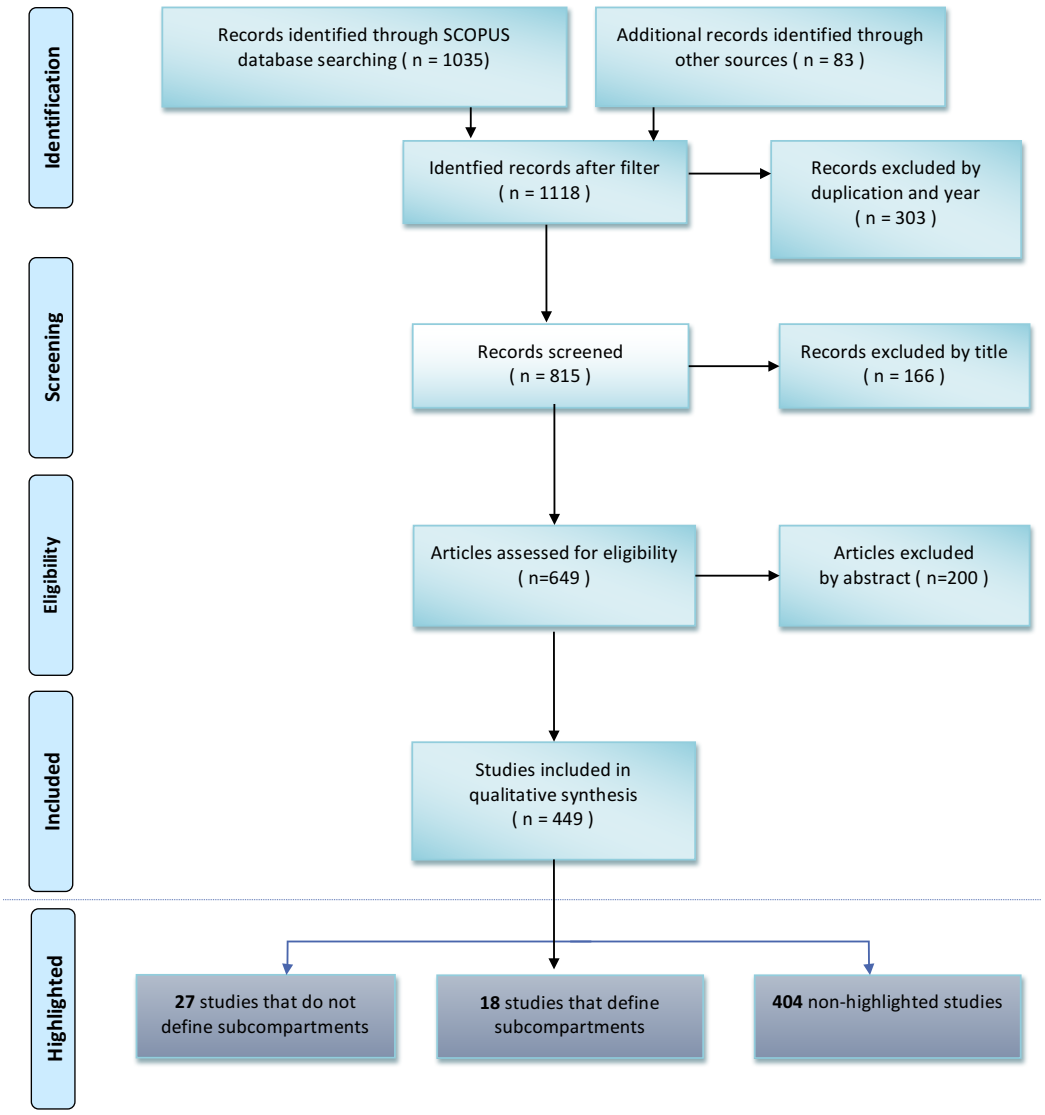
Identification
Screening
Eligibility
Included
Highlighted
Records identified through SCOPUS database searching (n = 1035)
Additional records identified through other sources (n = 83)
Identfied records after filter (n = 1118)
Records excluded by duplication and year (n = 303)
Records screened (n = 815)
Records excluded by title (n = 166)
Articles assessed for eligibility (n=649)
Articles excluded by abstract (n=200)
Studies included in qualitative synthesis (n = 449)
27 studies that do not define subcompartments
18 studies that define subcompartments
404 non-highlighted studies

Fig. 1

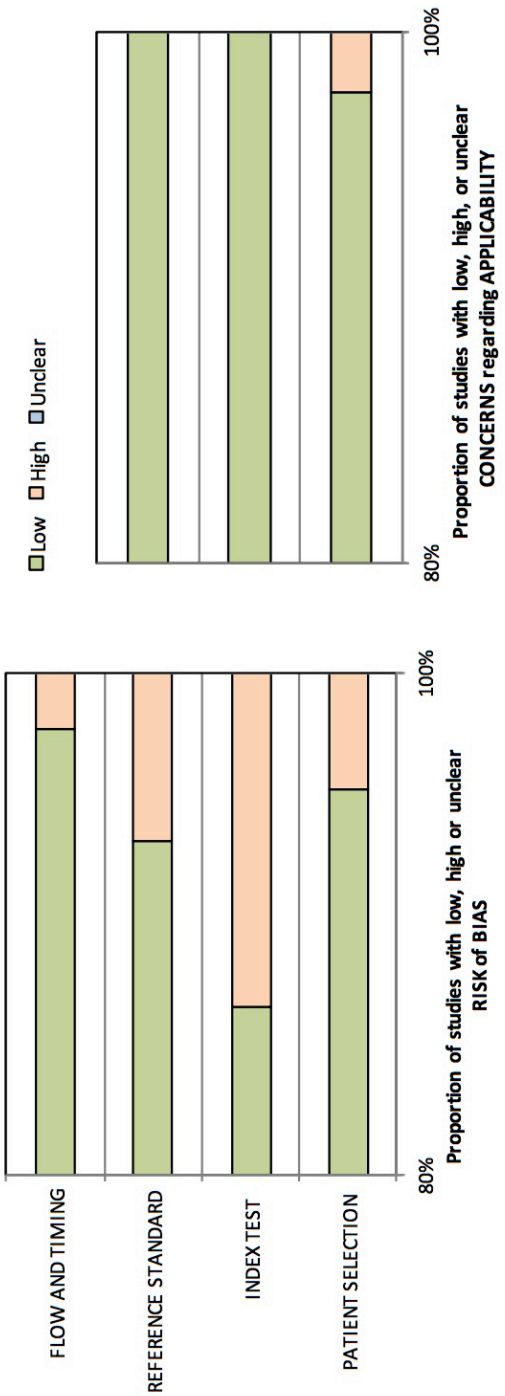
Low
High
Unclear
100%
80%
Proportion of studies with low, high, or unclear
CONCERNS regarding APPLICABILITY
100%
80%
Proportion of studies with low, high or unclear
RISK of BIAS
FLOW AND TIMING
REFERENCE STANDARD
INDEX TEST
PATIENT SELECTION

Fig. 2

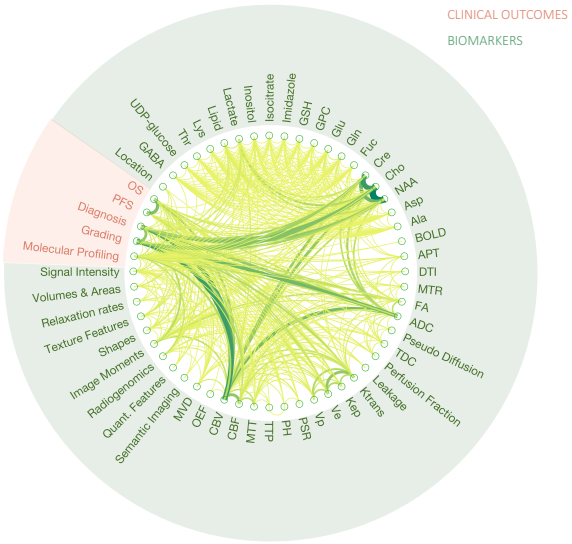
CLINICAL OUTCOMES
BIOMARKERS
Location
OS
PFS
Diagnosis
Grading
Molecular Profiling
Signal Intensity
Volumes & Areas
Relaxation rates
Texture Features
Shapes
Image Moments
Radiogenomics
Quant. Features
Semantic Imaging
MVD
OEF
CBV
CBF
MTT
TTP
PH
PSR
Vp
Ve
Kep
Ktrans
Leakage
Perfusion Fraction
TDC
Pseudo Diffusion
ADC
FA
MTR
DTI
APT
BOLD
Ala
Asp
NAA
Cho
Cre
Fuc
Gln
Glu
GPC
GSH
Imidazole
Isocitrate
Inositol
Lactate
Lipid
Lys
Thr
UDP-glucose
GABA

Fig. 3

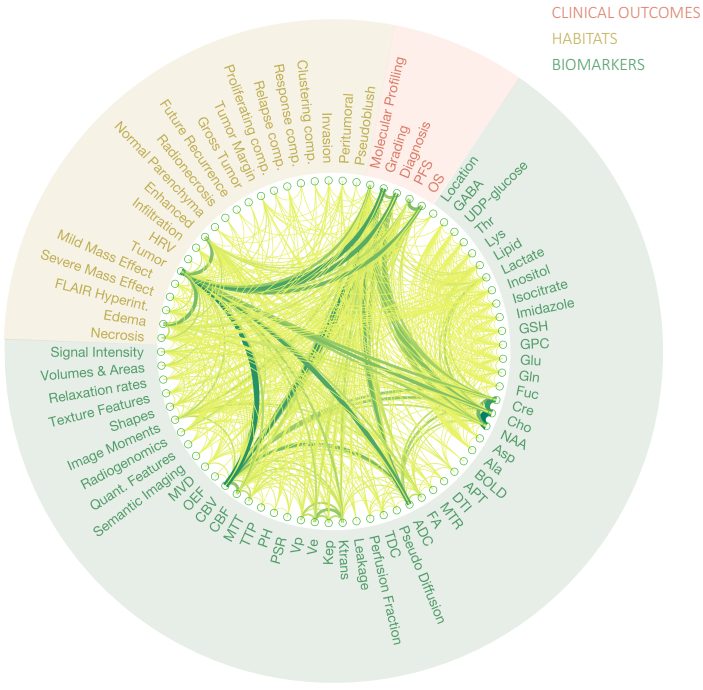
CLINICAL OUTCOMES
HABITATS
BIOMARKERS
Location
OS
PFS
Diagnosis
Grading
Molecular Profiling
Pseudolush
Peritumoral
Invasion
Clustering comp.
Response comp.
Relapse comp.
Proliferating comp.
Tumor Margin
Gross Tumor
Future Recurrence
Radionecrosis
Normal Parenchyma
Enhanced
Infiltration
HRV
Tumor
Mild Mass Effect
Severe Mass Effect
FLAIR Hyperint.
Edema
Necrosis
Signal Intensity
Volumes & Areas
Relaxation rates
Texture Features
Shapes
Image Moments
Radiogenomics
Quant. Features
Semantic Imaging
MVD
OEF
CBV
CBF
MTT
TTP
PH
PSR
Vp
Ve
Kep
Ktrans
Leakage
Perfusion Fraction
TDC
Pseudo Diffusion
ADC
FA
MTR
DTI
APT
BOLD
Ala
Asp
NAA
Cho
Cre
Fuc
Gln
Glu
GPC
GSH
Imidazole
Isocitrate
Inositol
Lactate
Lipid
Lys
Thr
UDP-glucose
GABA

Fig. 4

FEATURES EXTRACTED	#SOURCE PAPERS	CATEGORIZED VALUES *
POPULATION	368	Adult, Children, Animal
N (COHORTS)	395	-
STUDY DESIGN	449	Transversal/Longitudinal, Retro/Prospective
DIAGNOSIS	449	HGG, LGG, Diffuse Glioma, Recurrent Glioma, Metastasis
TREATMENT	356	Surgery, Radiotherapy (RT), Chemotherapy (CT)
CLINICAL OUTCOMES	442	OS, PFS, Diagnosis, Grading, Molecular profiling, etc.
MANAGEMENT MOMENT	346	Pre, Intra, Postoperative, PostRT, PostCT, Follow-up, Recurrence
MRI EXAM	449	Morphologic, Perfusion, Diffusion
ANALYSIS TECHNIQUES	430	Quantification, Manual Segmentation, Survival Analysis, ROC Curve, etc.
MR BIOMARKERS	449	CBV, CBF, ADC, FA, Metabolite concentrations, etc.
SUBCOMPARTMENTS	248	Tumor, Necrosis, Edema, Contrast-enhanced, Peritumoral, etc.
STATISTICAL TEST	319	Correlations, Student t-Test, COX, Mann-Whitney-Wilcoxon test, Kaplan-Meier, etc.

Table 1

Relevance (score)	Number of Papers
1	1
2	6
3	13
4	13
5	55
5,5	14
6	97
6,5	61
7	109
7,5	35
8	33
8,5	3
9	9
Total	449

Table 2

Table 3

Author	Population	N (Cohorts)	Study design	Diagnosis and Treatment	Clinical Outcome	Management moment	MRI exam	Analysis technique	MR biomarkers
Prager et al. [11]	Adult	68 (treatment related changes vs. recurrent tumor vs. mixed)	Transversal, Retrospective	GBM, Surgical resection followed by radiation therapy and temozolomide	Recurrence	Recurrence	DWI, DSC, T1, T2, FLAIR, T1c	Manual segmentation on ADC and DSC maps	ADC, CBV
Kickingereder et al. [12]	Adult	119 (discovery: 79; validation: 40	transversal, retrospective	GBM, No treatment	OS, PFS	Preoperative	T1c, FLAIR	Supervised principal component analysis	12190 features extracted: first-order moments, volume, shape, and texture features
Yoo et al. [13]	Adult	29 (12 GBM, 3 AA, 5 recurred GBM, and 9 lymphoma)	transversal, retrospective	HGG, LGG, lymphomas; Pretreatment	Diagnosis, Grading	Preoperative	ASL, CSI	Manual segmentation, quantification, ROC	Fractional Anisotropy, RA, Cho/Cr, and Cho/NAA
Liberman et al. [14]	Adult	13	Longitudinal, Retrospective	GBM; Resection, Chemoradiotherapy, Bevacizumab	Recurrence, Response to treatment	Follow-up, Recurrence	T1, T2, FLAIR, T2*, T1c, T2c*, MRS	Quantitative shape features, regression/correlation, survised classification	Tumor volume, shape features
Ramadan et al. [15]	Adult	12 (healthy control: 6; GBM: 6)	Transversal, Prospective	GBM, No Treatment	Molecular Profiling	Pretreatment	MRS	Peak volume ratios	Mobile lipids, Alanine, NAA, Œ≥-aminobutyric acid, glutamine and glutamate, glutathione, aspartate, lysine, threonine, total choline, glycerophosphorylcholine, myo-inositol, imidazole, uridine diphosphate glucose, isocitrate, lactate, and fucose
Hu et al. [16]	Adult	31 (recurrent tumor: 15 vs radiation necrosis: 16)	Transversal, Retrospective	GBM, radiation therapy after surgical resection	Molecular profiling	Postradioterapy	T1, T1c, T2, FLAIR, DSC, DWI, PD	Support Vector Machines ROC	CBV, CBF, ADC
Ingrisch et al. [17]	Adult	66	Transversal, Retrospective	GBM, No treatment	OS	Preoperative	T1c	manual segmentation, random survival forests (RSFs)	208 quantitative image features: tumor shape, signal intensity, and texture

Ulyte et al. [18]	Adult	69 (GBM: 49, AA: 20)	Transversal, Prospective	GBM, AA	PFS, OS	Preoperative	DCE	Histogram analysis, Univariate, multivariate, and Kaplan-Meier survival analysis	Ktrans, vp, ve, kep, IAUGC
O'Neill et al. [19]	Adult	12 (VEGF Trap treatment vs control)	Longitudinal, Retrospective	Temozolomide-resistant GBM, VEGF Trap	Response to treatment	Recurrence	Morphologic images, DCE DWI, FDG-PET	Time series	FDG-avidity, ADC, Ktrans, and ve
Kickingereder et al. [20]	Adult	152	Transversal, Retrospective	GBM, No treatment	Molecular profiling	Preoperative	Morphologic images, PWI, DWI	Histogram quantification, machine learning models	31 MRI features (volume ratios, ADC, CBF, CBV and intratumoral susceptibility signals, etc)
Sanz-Requena et al. [21]	Adult	39 (GIV: 31, GIII: 8)	Tranversal, Retrospective	HGG, Standard treatment (and partial)	Survival prediction	Preoperative	Morphological MRI, DSC	Manual segmentation, quantification, clustering, manual thresholding, survival analysis	Ktrans-T2* 10%
Jain et al. [22]	Adult	50	Transversal, Retrospective	GBM, Pretreatment	Molecular subtype, Genomic profile, OS	Preoperative	DSC	Manual Segmentation, Quantification, Survival Analysis, Regresion	CBV (maximum and mean)
Fathi et al. [23]	Human	13	Transversal, Retrospective	GBM	???	Preoperative	Morphologic, PWI, DWI	Supervised classification	Multivariate intensity space
Caulo et al. [24]	Human	118	Retrospective	Gliomas	Grading	Preoperative	Morphologic, DSC, DTI, MRS	Manual segmentation, Quantification, ROC	CBV, T2w signal intensity, diffusivity, Cho/Cr
Alexiou et al. [25]	Adults	30 (GBM: 27, AA: 2, AOD: 1)	Longitudinal, Retrospective	HGG, Surgery, radio- and chemotherapy	Recurrence	Follow-up	Morphologic, DSC, DTI, SPECT	Quantification, ROC	True diffusivity, ADC, Fractional Anisotropy, rMTT, Ktrans
van Cauter et al. [26]	Adult	35 (LGG:14, HGG:21)	Transversal, Prospective	Gliomas	Grading	Preoperative	T1, T2, DSC, DWI, CSI	Manual segmentation, quantification	Mean diffusivity, Fractional Anisotropy, kurtosis, CBF, MTT, relative decrease ratio, CSI metabolite ratios
Seeger et al. [27]	Adult	40	Transversal, Retrospective	Gliomas	HGG, Recurrence	Probably postsurgery	Morphological MRI, DSC, DCE, MRS	Quantification, ROC	CBV, CBF, Ktrans, Cho/Cr
Chawalparit et al. [28]	Adult	43	Transversal, Retrospective	Gliomas, Pretreatment	Diagnosis/Grading	Preoperative	Morphologic images, MRS, DTI, DSC	Manual segmentation, Quantification	Metabolites, CBV, CBF, ADC, Fractional Anisotropy
Li et al. [29]	Adult	64	Longitudinal, Retrospective	GBM; Resection, Chemoradiotherapy	PFS, OS	Postsurgery	CSI	Manual segmentation, Quantification, Regression analysis, Survival analysis	NAA/Cho, Cho/NAA

Shankar et al. [30]	Adult	20 Transversal, Retrospective	HGG	Pretreatment	Diagnosis, Grading	Preoperative	Morphological MRI, Perfusion CT	Manual segmentation, Quantification, ROC, Survival analysis	Permeability surface area, CBV
Zinn et al. [31]	Adult	78 (Discovery: 39, Validation: 39)	Transversal, Retrospective	GBM, treatment-naѵØve	OS, Molecular Profiling, Cell invasion	Preoperative	FLAIR	Kaplan-Meier survival statistics, microRNA-gene correlation analyses, and GBM molecular subtype-specific distribution	FLAIR hiper- and hipo-intensity volumes
Matsusue et al. [32]	Adult	15	Transversal, Retrospective	Glioma progression	Progression	Postradiotherapy	DWI, DSC, MRS	Quantification	ADC, CBV, Cho/Cr, Cho/NAA
Juan-Albarracin et al. [33]	Adult	31	Transversal, Retrospective	GBM	Segmentation	Preoperative	T1, T2, T1c, FLAIR	unsupervised segmentation	Multivariate intensity space
Itakura et al. [34]	Human	165	Transversal, Restrosective	GBM	Molecular signaling pathways	Preoperative	Morphologic images	Manual segmentation, Unsupervised classification	Shape, texture, and edge sharpness
Ion-Margineanu et al. [35]	Human	29 (Progression, No progression)	Transversal, Retrospective	GBM	Progression	Follow-up	Morphologic images, DWI, PWI, MRS	Manual segmentation, supervised classification (random forests, LogitBoost, or RobustBoost)	27-feature vector
Durst et al. [36]	Adult	10	Transversal, Prospective	Diffuse LGG, No Treatment	Nuclear density	Stereotactic biopsy	Morphologic, PWI, DTI	Quantification, PCA, regression analysis	Diffusivity, ADC, fractional anisotropy, rMTT, Ktrans
Yoon et al. [37]	Adult	60 (LGG: 12, HGG: 48)	Transversal, Retrospective	LGG, HGG, No treatment	Grading	Preoperative	Morphologic, DSC, DWI, MRS, FDG-PET	Quantification	ADC, CBV, Cho/Cr, Lip, Lac, SUVmax

Table 4

Author, Reference	Population	N (Cohorts)	Study design89	Diagnosis and treatment	Clinical Outcome	Management moment	MRI exam	Analysis technique	MR biomarkers	Habitats
Demerath et al.[38]	Adult	26	Transversal, Retrospective	GBM, No treatment	Molecular Profiling	Preoperative	T1c, FLAIR, PWI, DWI, CSI	Correlation	CBV, Axial diffusivity, Mass effect, mI	Peritumoral region, infiltration, severe mass effect, mild mass effect, adjacent normal-appearing matter, FLAIR hyperintensity, edema, necrosis, contrast enhanced tumor

Qin et al. [39]	Adult	10 (Beneficial vs non-beneficial)	Longitudinal, Retrospective	GBM, immune checkpoint blockade	Survival	Recurrence	T1c, FLAIR, ADC	correlation	Bidirectional diameters, T1c VOI, FLAIR VOI, IADC VOI, RANO	VOIs representing measurable abnormality suggestive of tumor on T1c, FLAIR and ADC
Boult et al. [40]	Mice	27 (RG2: 13, MDA-MB-231 LM2-4: 14)	Transversal, Prospective	Rat RG2 gliomas and human MDA-MB-231 LM2-4 breast adenocarcinomas in mice, No treatment	Molecular Profiling	Preoperative	T2, Gd-DTPA and ultrasmall superparamagnetic iron oxide (P904)-enhanced imaging	histogram, k-means	vascular parameters, water diffusion characteristics and invasion, fractional blood volume, ADC	1) Low fBV and relatively impermeable blood vessels (at the tumor margins), 2) high levels of water diffusion and low vascular permeability and/or fBV corresponded to regions of invasion and edema. 3) Mismatch between vascular permeability and blood volume
Server et al. [41]	Adult	74	Transversal, Retrospective	Gliomas, No treatment	Grading	Preoperative	DWI, CSI	Logistic regression, ROC curve analysis	ADC, Cho/Cr, Cho/NAA	Peritumoral edema, Tumor
Chang et al. [42]	Adult	26	Transversal, Retrospective	GBM, Inmediately after gross total tumor resection	Recurrence	Postsurgery	DWI, FLAIR	Logistic regression	ADC, FLAIR intensity	Areas of future GBM recurrence within the peritumoral region
Cui et al. [43]	Adult	108 (Development: TCGA, Validation: TCGA and internal	Transversal, Retrospective	GBM, No treatment	Overall Survival, Molecular Profiling	Preoperative	T1c, DWI	Kernel density estimation, MIPAV, Radiogenomic analysis,	High T1c intensity, low ADC	Gross tumour volume, High-risk volume (intratumoral subregion)
Khalifa et al. [44]	Adult	25 (Relapse: 13, Control: 12)	Longitudinal, Prospective	GBM, Radioteraphy, concominant chemotherapy	Recurrence	Follow-up	DSC, Last MR acquisition (last), last-(2M,4M,6M)	times series, ROC	Variations of 11 perfusion biomarkers	Hypoperfused tumor volume as marker of relapse
Prasanna et al. [45]	Adult	65 (short-term: 29, long-term: 36)	Transversal, Retrospective	GBM, no treatment	Overall Survival	Preoperative	T1c, T2, FLAIR	Expert manually segmented, radiomics	402 radiomics features for each region	Peritumoral region, enhancing lesion, necrosis
Lemasson et al. [46]	Adult	44 (GIV:36, GIII: 8)	Longitudinal, Retrospective	HGG, Standard treatment	Overall survival	Chemotherapy	T1c, FLAIR, DSC	statistical test, physiological segmentation, parametric response mapping (PRM)	CBV	PRM Compartments: increase, decrease and no change
Inano et al. [47]	Adult	36 (HGG: 21, LGG: 15)	Transversal, Retrospective	Gliomas, no treatment	Grading	Preoperative	T1, T2, FLAIR, T1c	Self-organizing maps, k-means	161 radiomics features	12-class MRcIs (magnetic resonance-based clustered images)

Delgado-Goni et al.[48]	Female C57BL/6 mice (animal)	3812	Transversal, Prospective	GBM, Temozolamide	Response to treatment	Postchemoteraphy	CSI	Semi-supervised source extraction	Mobile lipids and polyunsaturated fatty acids	Normal brain parenchyma, actively proliferating GBM and GBM responding to treatment)
Cui et al. [49]	Adult	79 (Discovery:46, Validation: 33)	Transversal, Retrospective and prospective	GBM, No treatment	Overall Survival	Preoperative	T1c, FLAIR	Automated intratumor segmentation, Multivariate sparse Cox regression model	Quantitative imaging features	Spatially distinct subregions by multiparemtric intensity patterns
Price et al. [50]	Adult	50	Transversal, Retrospective	GBM, no treatment	Invasive and non-invasive regions	Preoperative	Morphologic imagesm, DTI, DSC, CSI	Image corregistration	CBV, NAA, mI, Cho, Glx, Cr	Invasive region, noninvasive region, and normal parenchyma
Sauwen et al. [51]	Adult	35 (Gent: 21, Leuven: 14)	Transversal, Retrospective	HGG, no treatment	Segmentation	Preoperative	Morphologic images, PWI, DWI, CSI	Unsupervised classification, Hierarchical non-negative matrix factorization	Multiparametric space	hNMF sources, Tissue class mixtures
Jena et al. [52]	Adult	26 (recurrence: 19, radiotion necrosis: 7).	Transversal, Retrospective	Gliomas, Surgery and radiation	Recurrence vs Radiation Necrosis	Postradiotherapy	Morphologic images, DSC, ADC, PET	Multiparametric analysis	Target-to-background ratio, Cho/Cr CBV, ADC	Maximal contrast enhancement, FET uptake
Kim et al. [53]	Adult	169 (Recurrence: 87, Radiation necrosis: 82)	Transversal, Retrospective	GBM, standard treatment	Recurrence	Follow-up (post-treatment)	T1, DSC, DCE, DWI	Quantification, ROC	ADC, CBV, IAUC	Radionecrosis, tumor
Christoforidis et al. [54]	Adult	35	Transversal, Prospective	Gliomas, no treatment	Diagnosis, microvessels area	Preoperative	Morphologic images (GRE sequence)	Supervised classification	Microvessel density, microvessel size	Tumoral pseudoblush
Wang et al. [55]	Adult	67 (GBM: 26, SBM: 25, PCL: 16)	Transversal, Retrospective	GBM, SBM, PCL	Diagnosis, No treatment	Preoperative	DTI, DSC	2-level decision tree	Fractional anisotropy, ADC, CL, CP, CS, CBV	Enhancing, immediate peritumoral and distant peritumoral regions