Review

Current Evidence, Limitations and Future Challenges of Survival Prediction for Glioblastoma Based on Advanced Noninvasive Methods: A Narrative Review

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Abstract: Background and Objectives: Survival estimation for patients diagnosed with Glioblastoma (GBM) is an important information to consider in patient management and communication. Despite some known risk factors, survival estimation remains a major challenge. Novel non-invasive technologies such as radiomics and artificial intelligence (AI) have been implemented to increase the accuracy of these predictions. In this article, we reviewed and discussed the most significant available research on survival estimation for GBM through advanced non-invasive methods.

Materials and Methods: PubMed database was queried for articles reporting on survival prognosis for GBM through advanced image and data management methods. Articles including in their title or abstract the following terms were initially screened: ((glioma) AND (survival)) AND ((artificial intelligence) OR (radiomics)). Exclusively English full-text articles, reporting on humans, published as of 1 September 2022 were considered. Articles not reporting on overall survival, evaluating the effects of new therapies or including other tumors were excluded. Research with a radiomics-based methodology were evaluated using the radiomics quality score (RQS).

Results: 382 articles were identified. After applying the inclusion criteria, 46 articles remained for further analysis. These articles were thoroughly assessed, summarized and discussed. The results of the RQS revealed some of the limitations of current radiomics investigation on this field. Limitations of analyzed studies included data availability, patient selection and heterogeneity of methodologies. Future challenges on this field are increasing data availability, improving the general understanding of how AI handles data and establishing solid correlations between image features and tumor’s biology.

Conclusions: Radiomics and AI methods of data processing offer a new paradigm of possibilities to tackle the question of survival prognosis in GBM.

Keywords: glioblastoma; glioma; high-grade glioma; radiomics; artificial intelligence; deep learning; machine learning; survival

1. Introduction

Glioblastoma (GBM), with an incidence of 3.5/100,000 population, is the most common malignant primary neoplasm of the brain in adults [1]. Its fatal prognosis has scarcely improved over the last decades despite intensive research in the field [1]. Some clinical, surgical and radiological features are known independent predictors of survival [2]. However, accurate survival prediction is a key challenge for patients, relatives and physicians in their search for precision medicine strategies to tackle the burden of this devastating tumor [3].

A radiology-based approach to prognosis prediction has gained momentum in recent years fostered by the development of advanced tools to manage an immense quantity of data and thanks to its noninvasiveness, radiomics, a science based on quantitative data mining from medical images, has been extensively used in oncology [4]. Texture analysis, a branch of radiomics, exploits the information concealed in voxels and pixels and provides a quantitative assessment of images that might serve as a virtual biopsy [5].
Thus, different imaging modalities, segmentation algorithms and texture features have successfully contributed to supporting tumor diagnosis, molecular profile estimation, treatment response evaluation and overall survival (OS) prediction in neurooncology [6–8].

Handling such an enormous quantity of complex data as derived from radiomic analysis requires specific methods to obtain useful results and interpretable information. Thus, artificial intelligence (AI) methods have been developed and applied to this novel prognostic approach [9]. Machine learning (ML), a discipline within AI, through training datasets on ground truth labels has allowed us to obtain algorithms that can execute complex tasks such as tumor segmentation, tumor grading, molecular classification and survival prognosis [10]. ML may follow a supervised (e.g., logistic regression, support vector machine (SVM), random forest (RF), naïve Bayesian networks, decision trees (DT)) or unsupervised (e.g., K-means cluster) workflow. In a different way, deep learning (DL), a subclass of ML, does not require human intervention or ground truth labels to learn. Instead, DL, mainly present in different forms of neural networks (NN), has been successfully applied to tasks such as survival estimation, tumor segmentation, and estimation of glioma molecular subtypes [6,11–15]. NN learns on its own from previous fails and successful associations and can make more complex correlations. However, DL needs higher volumes of data and requires extensive computational time for training. In all, different AI strategies might be used to perform similar functions, which in the case of survival prognosis often consists of correctly classifying patients into long and short survivors, whether by means of SVM, RF, DT or naïve Bayesian classifiers, for instance, in the case of ML; or NN in the case of DL.

In this review, we present an update of the current evidence on advanced statistics, radiomics and data processing methods for the accurate survival prognosis of patients suffering from high-grade gliomas. The initial attempt to conduct a systematic review or meta-analysis was soon quit given the enormous heterogeneity of methods, the frequent involvement of the same set of patients from public datasets and the lack of consistency in results reporting. Instead, we sought to provide a comprehensive and thorough review of advanced noninvasive methods for survival estimation in GBM, while we discuss present challenges and future perspectives in this field.

2. Materials and Methods

A systematic search of PubMed was performed for articles reporting on the survival prognosis for GBM, involving in their methodology a noninvasive advanced radiological approach including radiomics and/or AI.

The query was built for the following terms to be present on the Title or abstract: ((glioma) AND (survival)) AND ((artificial intelligence) OR (radiomics)). Only English full-text articles, reporting on human subjects, published (even ahead of print) as of 1 September 2022 were considered. Each manuscript was independently reviewed by two authors (S. G-G and S.C.). Articles not reporting on overall survival, including other tumors than GBM, or redundant articles were excluded. Articles assessing the effect of novel therapies on survival were also excluded. In the case of an investigation conducted by the same scientific team with similar methods applied to an updated, previously published dataset, the last manuscript was considered. In case of disagreement on the need to include a given study, a consensus was reached after substantiated discussion held by the signing authors.

Studies involving a methodology based on radiomics were assessed according to the radiomics quality score (RQS) [16]. The RQS is a sixteen-item scale that evaluates the methodology and reporting of an investigation to improve the consistency of radiomics studies, increase its reproducibility and enhance scientific soundness in this field [16].

3. Results

The search resulted in 382 articles with the terms glioma, survival, AI and radiomics, whether in their title or abstract. After applying the inclusion criteria, 311 articles were excluded. Seventy-one full-text articles were thoroughly reviewed, of which 46 articles
were ultimately included (Figure 1). The main results of these articles are summarized in Table 1. Similarly, the results of the RQS of articles, whose methodology was based on radiomics, are presented in Table 2. The average and median scores of the RQS for the analysed studies were 10.5 (29%) and 11 (31%), respectively.

Figure 1. Flowchart depicting the identification, screening and inclusion of studies in the present review.
Table 1. Summary of the studies analyzed in this review.

| Author          | Year | N  | Cases from Public Database | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Type                                | Feature Selection/ML Classifier | Validation Method | Model Performance |
|-----------------|------|----|----------------------------|--------------------------------|-----------------------------|---------------------|-----------------------|---------|-------------------------------------------|-------------------------------|------------------|-------------------|
| Yang [17]       | 2015 | 82 | Yes                        | TCIA                           | T1C FLAIR                   | Manual Enhancing tumor Whole tumor | Intensity Normalization Re-Slicing | MATLAB  | 976 | SFTA, GLRLM, Local Binary Patterns, Histogram of oriented gradients, Haralick | RF                           | Out-Bag Validation | SFTA T1C AUC = 0.69 |
| Chaddad [18]    | 2016 | 40 | Yes                        | TCIA                           | T1 FLAIR                    | Manual Enhancing Tumor Necrosis Edema | Co-Registration Intensity Normalization | MATLAB  | 22 | GLCM                                        | DA, NB, DT, SVM              | LOOCV            | AUC = 0.793 Phenotypes with KM significantly different |
| Liu [19]        | 2016 | 68 | No                         | RS-F-MRI                        | DTI T1 T2 FLAIR DSI T1 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MITK | 12,190 | First order, volumetric, Wavelet, Haralick, GLCM, GLRLM, SPCA | SVM                          | 10-FoldCV         | Retrospective Accuracy = 77.14%, Prospective Accuracy = 79.17% |
| Macyszyn [20]   | 2016 | 134| No                         | TCIA                           | T1 C1 T2 FLAIR DSI T1 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MATLAB  | 18 | First order, GLCM, Haralick                  | Univariate Analysis            | No               | AUC = 0.83 HR = 0.019 KM |
| Kickingereder [21] | 2016 | 119| No                         | T1 C1 T2 FLAIR DSI-FLAIR DWI DSI-C | T1 C1 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MITK | 12,190 | First order, volumetric, Wavelet, Haralick, GLCM, GLRLM, SPCA | SVM                          | 10-FoldCV         | Retrospective Accuracy = 77.14%, Prospective Accuracy = 79.17% |
| Lee [22]        | 2016 | 24 | Yes                        | TCIA                           | DS-C                        | Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration Normalization | MATLAB  | 18 | First order, GLCM, Haralick                  | Univariate Analysis            | No               | AUC = 0.83 HR = 0.019 KM |
| Ingrisch [23]   | 2017 | 66 | No                         | T1 C1 T2 FLAIR DSI-FLAIR DWI DSI-C | T1 C1 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MATLAB  | 208 | First order, Haralick, Parameter-free Threshold Adjacency Statistics | Minimal Depth, RF              | 10-FoldCV         | C-index = 0.67 HR = 1.08 KM |
| Liu [24]        | 2017 | 133| Yes                        | TCIA                           | T1 C1 T2 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MATLAB  | 56 | First order, GLCM, GLRLM                    | RFE-SVM                      | 10-FoldCV         | AUC = 0.81 Accuracy = 78% KM |
| Li [25]         | 2017 | 92 | Yes TCIA = 60              | TCIA                           | T1 C1 T2 FLAIR DSI-FLAIR DWI DSI-C | Automated Anatomical Labelling Automated Enhancing Tumor Non/Enhancing Tumor Edema Ventricles Semiautomatic, Enhancing Tumor Non/Enhancing Tumor Normal WM Manual Enhancing tumor Nonenhancing tumor Normal WM | Co-Registration N4 bias Correction Intensity Normalization | MATLAB  | 45,792 | First order, GLCM, GLRLM, GLSZM, NCTDM | LASSO                        | 10-FoldCV         | C-index = 0.71 HR = 1.29 KM |
| Author       | Year | N   | Cases from Public Database | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Selection/ML Classifier | Validation Method | Feature Performance |
|-------------|------|-----|----------------------------|--------------------------------|-----------------------------|---------------------|------------------------|---------|-------------------------------|-------------------|---------------------|
| 10 Liu [24] | 2017 | 133 | Yes                        | T1 | T1C | Manual Whole Tumor N4 Bias correction Resampling | MATLAB | 56 | GLCM, GLRLM, Histogram | SVM    | Accuracy = 78.2% AUC = 0.8104 |
| 11 Lao [15] | 2017 | 112 | Yes                        | T1 | T1C | Manual Necrosis Edema | MATLAB | 99,707 | First order, GLSM, GLRLM, GLSZM, NGTDM, Deep features | LASSO | HR = 5.13 KM Nomogram |
| 12 Prasanna [26] | 2017 | 65  | Yes                        | T1 | T1C | Manual Enhancing Tumor Necrosis Edema | MATLAB | 402 | Haralick, Laws features, Histogram of oriented gradients, Laplacian pyramids | mRMR, RF | 3-FoldCV KM C-index = 0.70 |
| 13 Kickingreder [27] | 2018 | 181 | No                         | T1 | T1C | Semi-automatic, Enhancing Tumor Nonenhancing Tumor Necrosis Manual | MITK  | 1043 | First order, shape, GLCM, GLRLM, GLSZM | LASSO | VD = 61 HR = 2.72 |
| 14 Bae [28] | 2018 | 217 | No                         | T1 | T1C | Enhancing Tumor Non/Enhancing Tumor Necrosis Manual | Python | 796 | Volumetric, Shape, First order, GLCM, Gabor texture | VHA, RSF | VD = 54 AUC = 0.652 KM |
| 15 Sanghani [29] | 2018 | 163 | Yes                        | T1 | T1C | Enhancing Tumor Non/Enhancing Tumor Necrosis Edema | Python | 2200 | Texture features based on LOG filter | RFE-SVM | 5-FoldCV Accuracy = 98.7% |
| 16 Chaddad [30] | 2018 | 40  | Yes                        | T1 | T1C | Manual Enhancing Tumor Non/Enhancing Tumor Necrosis Edema | MATLAB | 9 | SVM-RFE | RF 5-FoldCV AUC = 0.85 |
| 17 Liu [31] | 2018 | 119 | Yes                        | T1 | T1C | Manual Enhancing tumor | MATLAB | 54 | First order, GLCM, GLRLM | SVM-RFE | No |
| 18 Molina-Garcia [32] | 2019 | 404 | Yes                        | T1 | T1C | Manual Enhancing Tumor Necrotic Core Manual Whole tumor Edema Contralateral WM | No | 44 | First Order GLRLM, GLCM | NN SVM RT | VD = 93 C-index = 0.817 (Optimal Linear Prognosis Model) Radiomics |
| 19 Tan [33] | 2019 | 147 | Yes                        | T1 | T1C | Manual Whole tumor Edema Contralateral WM | MATLAB | 1456 | LASSO | VD = 35 C-index = 0.76 |
| Author | Year | N | Cases from Public Database | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Type | Feature Selection/ML Classifier | Validation Method | Model Performance |
|--------|------|---|----------------------------|-------------------------------|-----------------------------|--------------------|----------------------|--------|-------------|-------------------------------|-----------------|-------------------|
| Nie [34] 2019 | 93 | No | T1C | T1C | T2 | Manual Whole Tumor | Co-Registration | N/A | CNN supervised | | CNN SVM | Accuracy = 90.46% (VD = 88%) C-index 0.659 KM HR = 3.65 AUC = 0.82 KM HR = 1.62 High and Low risk Log Rank Test p = 0.004 |
| Choi [35] 2019 | 114 | Yes TCIA = 53 | T1C | T1C | T2 | Manual Peritumoral | N/A | Python | First Order, GLCM, GLRLM, GLSZM | No | VD = 34 |
| Chen [36] 2019 | 127 | Yes TCIA | T1C | T1C | T2 | Manual Enhancing tumor | Insensity Normalization | MATLAB | 3824 | First order, Shape, GLCM, GLRLM | mRMR | N/A |
| Sasaki [37] 2019 | 182 | No | T1 | T1C | T2 | Manual Enhancing tumor | Whole tumor | Co-Registration | Intensity Normalization | MATLAB | 489 | First order, GLCM, GLRLM, shape | SPCA, LASSO | 10-FoldCV |
| Um [38] 2019 | 161 | Yes TCIA | T1 | T1C | FLAIR | Semiautomatic Whole tumor | Co-Registration | Rescaling Bias field Correction Histogram Matching Resampling | CERR | 420 | First order, Edge features (LoG, Sober, Gabor, Wavelet), GLCM, GLSZM, Haralick | LASSO | VD = 47 | HR = 3.61 KM |
| Chang [39] 2019 | 12 | No | T2/FLAIR Pretreatment Posttreatment | T1C | FLAIR | Manual Whole Tumor | Co-Registration | MATLAB | 61 | GLCM, GLDM, GLRLM, GLSZM, Delta Radiomics | RF, Linear- SVM, Kernel-SVM, NN, NB, LR | No | AUC = 0.889 Best Result: RF with SVM and NN with Delta Radiomics |
| Tixier [40] 2019 | 159 | Yes TCIA = 47 | T1C | T1C | FLAIR | Semiautomatic Whole tumor | Co-Registration | Gabor Filtering Binning | CERR | 286 | First order, GLCM, GLSZM, Delta Radiomics | LASSO | VD = 61 | KM |
| Shboul [41] 2019 | 224 | Yes BRATS | T1C | T1C | FLAIR | T2 | Manual Whole tumor | Co-Registration | Gabor Filtering Binning | N/A | 31,000 | Texture, Euler, Histogram | Univariate, RFS, RF, XGBoost | LOOCV | Accuracy = 73% | VD-Accuracy = 68% |
| Chaddad [42] 2019 | 200 | Yes TCIA = 71 | T1C, FLAIR | T1C, FLAIR | T2 | Manual Whole tumor | Resampling | MATLAB | 45 | First order, GLCM, NGTDM, GLSZM | No | VD = 100 | AUC = 0.752 KM DTI Radiomics AUC = 0.70 C-index 0.63 DS-C AUC = 0.76 C-index = 0.55 |
| Kim [43] 2019 | 83 | No | T1C, FLAIR | T1C, FLAIR | T2 | Manual Whole tumor | Co-Registration | Intensity Normalization Resampling | MATLAB | 6472 | First order, Wavelet, GLCM, GLRLM | LASSO | 10-FoldCV | |
Table 1. Cont.

| Author Year | N  | Cases from Public Database | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Type | Feature Selection/ML Classifier | Validation Method | Model Performance |
|-------------|----|----------------------------|--------------------------------|----------------------------|---------------------|-----------------------|--------|--------------|----------------------------------|------------------|---------------------|
| Liao [44] 2019 | 137 | Yes TCIA | FLAIR | Manual | N/A | Python | 72 | First order, GLCM, GLSZM, GLRLM, NGTDM, GLDM | GBDT, SVM, kNN | VD = 41 | Accuracy = 81% Short survival AUC = 0.79 Long survival AUC = 0.81 Accuracy = 57.8% Short survival AUC = 0.81 Median survival AUC = 0.47 Long survival AUC = 0.72 |
| Osman [45] 2019 | 163 | Yes, BRATS | T1 TIC FLAIR T2 | Manual Enhancing Tumor Non/Enhancing Tumor Edema | Co-Registration Smoothing Interpolation Intensity Normalization Intensity Rescaling | MATLAB | 147 | First order, GLCM, Histogram of oriented gradients, Local Binary Pattern. | LASSO, SVM, kNN, DA | VD = 54 | |
| Chaddad [46] 2019 | 73 | Yes TCIA | TIC FLAIR | Manual Enhancing Tumor Necrosis Edema | Co-Registration Resampling Intensity Normalization | MATLAB | 11 | JIM, GLCM | SpCoR RF | LOOCV | JIM features: HR = 1.88 AUC = 0.776 |
| Zhang [47] 2019 | 105 | Yes TCIA | T1 TIC FLAIR T2 | Manual FLAIR Signal Enhancing Tumor | Co-Registration Resampling CoUluvet Normalization | MATLAB | 4000 | First Order, GLCM, GLRLM, GLSZM, Wavelet | LASSO LR | VD = 35 | C-Index = 0.94 Nomogram |
| Han [6] 2020 | 178 | Yes TCIA = 128 | T1C | Manual Whole Tumor | Normalization Gray-Level Quantization Resampling | MATLAB (radiomics) CNN (Keras-TensorFlow) Elastic Net/Cox (R) | 8540 | First order, Nontexture, Histogram, GLCM, GLRLM, GLSZM, NGTDM Deep features(CNN) | MAD, C-Index, PearsonC | No | Long Rank Test Long/Short Survival p < 0.001 (HR = 3.26) |
| Zhang [48] 2020 | 104 | Yes TCIA | T1 TIC FLAIR T2 | Manual Whole Tumor subregions | Co-Registration Resampling Normalization | MATLAB | 180 | First Order, GLCM, GLRLM, GLSZM | Multiple Instance Learning, SVM 13 F selection (RelieF, GINI, CHSQ . . . ) and 12 ML methods (CNN, SVM, RF, DT . . . ) | VD = 33 | Accuracy = 87.9% Sensitivity = 85.7% Specificity = 89.4% 2-Class: AUC = 0.66 Accuracy = 64% 3-Class: AUC = 0.58 Accuracy = 38% |
| Suter [49] 2020 | 109 | Yes TCIA = 76 | T1 TIC FLAIR T2 | Co-Registration Skull Stripping Resampling N4 Bias Correction | Python | 8327 | First order, GLCM, GLSZM, GLRLM, NGTDM, GLDM, Deep features. | | VD = 76 | |
Table 1. Cont.

| Author | Year | N    | Cases from Public Database * | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Type | Feature Selection/ML Classifier | Validation Method | Model Performance |
|--------|------|------|-------------------------------|-------------------------------|-------------------------------|----------------------|-----------------------|---------|--------------|---------------------------------|------------------|-------------------|
| 37     | Bakas [50] | 2020 | 101 | No | T1 TIC FLAIR T2 DTI DSI-C | Automatic Enhancing Tumor Non/Enhancing Tumor Edema | Co-Registration Resampling, Noise Filtering Histogram Matching | CaPTk | 1612 | First order, Volumetric, Wavelet, GLCM, GLRLM, GLSZM, NGTDM, Spatial information, diffusion properties | Forward Selection, SVM | 5-FoldCV | Accuracy: Advanced MRI = 73%, Basic MRI = 74.3%, KM = 0.64 |
| 38     | Park [51]  | 2020 | 216 | No | T1 TIC FLAIR DWI DSI-C | Semiautomatic Enhancing tumor Semiautomatic Whole tumor Enhancing tumor Nonenhancing tumor Necrosis | Co-Registration Intensity Normalization Resampling | MATLAB | 1618 | First order, GLCM, GLRLM, Wavelet | LASSO | VD = 58 | C-index = 0.64, KM = 0.90 |
| 39     | Lu [52]   | 2020 | 181 | No | T1C | Manual Whole Tumor Manual Whole Tumor Enhancing tumor Tumor core | Co-Registration Intensity Normalization N4 Bias Correction | Python | 333 | Shape, First order, GLCM, GLRLM, GLSZM, NGTDM, VASARI | VHA, RFS | VD = 78 | AUC = 0.96, C-index = 0.09 |
| 40     | Baid [53]  | 2020 | 346 | Yes | BRATS T1 TIC FLAIR T2 | Automatic Enhancing Tumor whole Tumor Enhancing tumor Tumor core | Co-Registration Intensity Normalization Resampling | MATLAB | 678 | First order, Wavelet decomposition, GLCM | SpCoR, RF | VD = 53 | Accuracy = 57.1% |
| 41     | Moradmand [11] | 2021 | 260 | Yes | TCGA IVY | N/A | N/A | Python | N/A | Clinical, Tumor Data, PostSurgical Treatment, Molecular variables | CoxPH, RF, NN | TD = 78 | C-index = 0.823, Bayesian Hyperparameter Optimization |
| 42     | Yan [5]   | 2021 | 688 | Yes | TCIA CGGA Local | DTI T2 Flair | Manual Whole Tumor | Coregistration Standardization | Python | N/A | Radiogenomics Clinical | CNN | VD = 77 | C-index = 0.825 (VD-C-index = 0.79) |
| 43     | Priya [54] | 2021 | 85  | No | T1C | Manual Whole Tumor | N/A | TexRAD | 36 | Texture, Age | SVM, NN, RT | 5-FoldCV | AUC = 0.811, Accuracy = 67% AUC CV = 0.71 |
| 44     | Cepeda [55] | 2022 | Yes | TCIA = 34 BratS = 119 | T1 TIC FLAIR T2 | Hybrid (GLISTRBoost) Enhancing tumor Nonenhancing tumor Edema | Re-Orientiation Co-Registration Resampling Normalization | CaPTk | 15,720 | First Order, Histogram, Volumetric, Morphologic, GLCM, GLRLM, GLSZM, NGTDM | Gini Index, FCBF, InfoGain / LR, NB, kNN, RF, SVM, NN | TD = 60 | AUC = 0.98, Accuracy = 94% (TD-AUC = 0.77 TD-Accuracy = 80%), Naive Bayes |
| 45     | Ben Ahmed [14] | 2022 | 163 | Yes | BRATS T1C | Automatic Enhancing Tumor whole Tumor | Null-Voxel Reduction Data Augmentation 2D Transformation | Python | 35,709 | Snapshot | CNN | VD = 46 | Accuracy = 74% |
Table 1. Cont.

| Author Year | N | Cases from Public Database * | MRI Sequence Radiomics Analysis | Segmentation Method (Labels) | Image Preprocessing | F. Extraction Software | N of F. | Feature Type | Feature Selection/ML Classifier | Validation Method | Model Performance |
|-------------|---|-------------------------------|-------------------------------|-----------------------------|---------------------|-----------------------|--------|--------------|--------------------------------|-----------------|-------------------|
| Ruan [56] 2022 | 200 | Yes | TCGA = 129 | T1C, T1, T2FLAIR | Manual Whole Tumor | Standardization | MATLAB 3D Slicer | 665 | First Order, VASARI, GLCM, GLDM, GLSZM, NGTDM | LASSO | VD | Radiomics C-Index = 0.935 RadiomicsVASARI C-Index = 0.622 |

AUC: Area Under the Curve from Receiver Operating Characteristics; BraTS: Brain Tumor Segmentation Challenge Dataset; C: Contrast Enhanced; CGGA: Chinese Glioma Genome Atlas; CNN: Convolutional Neural Networks; CoxPH: Cox proportional hazards; CV: Cross Validation; DA: Discriminated Analysis; DS: Dynamic Susceptibility; DT: Decision Trees; DTI: Diffusion Tensor; DWI: Diffusion Weighted Image; Imaging; F: Radiomic Features; GBDT: Gradient Boosting Decision Tree; GLCM: Gray Level Co-Occurrence Matrix; GLDM: Gray Level Difference Matrix; GLSZM: Gray Level Size Zone Matrix; HR: Hazard Ratio; IVY: Ivy Glioblastoma Atlas Project; JIM: Joint Intensity Matrix; KM: Kaplan-Meier Survival Curves; kNN: K Nearest Neighbor; LASSO: Least Absolute Shrinkage and Selection operator; LOOCV: Leave One Out Cross Validation; LoG: Laplacian of Gaussian; LR: Logistic Regression; MAD: Median Absolute Deviation; mRMR: minimum Redundancy Maximum Relevance; N: Number of patients; NB: Naïve Bayesian; NGTDM: Neighborhood gray tobe difference matrix; NN: Neural Networks; PearsonC: Pearson’s Co-Relation Coefficient; RS-F-MRI: Resting State functional MRI; RF: Random Forest; RFE: Recursive feature elimination; RFS: Recursive Feature Selection; RT: Regression Trees; SPCA: Sparse Principal Component Analysis; SpCoR: Spearman’s Co-Relation; SFTA: Segmentation Fractal Texture Analysis; SVM: Support Vector Machine; TCGA: The Cancer Genome Atlas; TCIA: The Cancer Imaging Archives; TD: Testing Dataset; VD: Validation Dataset; VHA: Variable Hunting Algorithm; WM: White Matter. * (If all cases were from a public dataset, the number is not disclosed again).
Table 2. Itemized score for the Radiomics Quality Score of the included radiomics studies assessing survival prognosis in high grade gliomas.

| Author and Year | Yang 2015 | Lee 2016 | Kickingeder 2016 | Macyszyn 2016 | Chaddad 2016 | Lao 2017 | Liu 2017 | Li 2017 | Ingrisch 2017 | Prasanna 2017 | Bae 2018 | Sanghani 2018 | Liao 2018 | Chaddad 2018 | Liu 2018 | Choi 2019 |
|----------------|-----------|----------|------------------|---------------|-------------|---------|---------|---------|-------------|-------------|---------|-------------|---------|-------------|---------|-----------|
| Image protocol quality | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| Multiple segmentations | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Phantom study on all scanners | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Imaging at multiple time points | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Feature reduction or adjustment for multiple testing | -3 | 3 | 3 | 3 | -3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | -3 | 3 | -3 | -3 | -3 |
| Multivariate analysis with nonradiomic features | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 |
| Detect and discuss biologic correlates | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |
| Cutoff analysis | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Discrimination statistics | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 2 | 0 | 1 | 1 | 1 |
| Calibration statistics | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Prospective study registered in trial data base | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Validation | 2 | -5 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | -5 | 2 | 2 | 2 | 2 | 2 |
| Comparison with criterion standard | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 2 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 |
| Potential clinical utility | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cost-effectiveness analysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Open science and data | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D |
| Total points | 10 | 10 | 5 | 14 | 13 | 10 | 16 | 13 | 10 | 15 | 11 | 13 | 11 | 11 | 15 | 15 | 13 |
| % RQS | 28% | 28% | 14% | 39% | 36% | 28% | 44% | 36% | 28% | 42% | 31% | 36% | 31% | 31% | 42% | 42% | 36% |
4. Discussion

Predicting life expectancy for patients diagnosed with GBM is a major challenge. Many variables might influence the prognosis, and despite numerous efforts and approaches, uncertainty often erodes patients’ and physicians’ will to face and overcome the fateful outlook that this disease entails. New advanced techniques to process images and data have proven their ability to noninvasively mine and display the information shielded in the infinite number of pixels and voxels that compose multimodal neuroimages. Initially, we conducted a meta-analysis or systematic review of the main evidence on survival prognosis through these advanced methods, such as radiomics and AI. However, we soon realized that the tremendous variability of methods, the lack of consistency in reporting the results and the recurrent use of public datasets of the same patients hampered successful fulfillment of this task and rendered it unmanageable. Instead, we present a thorough review of the key available evidence regarding this critical issue while we discuss the main existing limitations, the actual room for improvement and the new horizons and challenges that future research should address.

Conventional morphological MRI features contain valuable prognostic information. As proven by Molina et al., a simple model based on age and morphological features, without texture data, could outperform more complex models in GBM prognosis prediction. Nonetheless, morphologic information might be a loose term in which many features fit. In an effort to unify the common characteristics gliomas display on MRI studies and to harmonize the vocabulary in which we refer to them, Visually Accessible Rembrandt Images (VASARI) were developed [57]. This list of 30 features has been demonstrated to be useful for predicting OS in GBM [58]. In addition, VASARI, which does not consider texture information, has been successfully integrated into ML models based on texture data [56]. However, in a study by Ruan et al., only cortical involvement was strongly associated with poor outcomes. Indeed, VASARI features did not increase the predictive accuracy of the RF model based on radiomic features when combined with them.

As shown in Table 1, there are several examples of predictive algorithms based on texture features extracted from conventional MRI sequences. Studies vary widely in terms of image preprocessing, segmentation methods, number of features and ML classifiers (Figure 2). Different strategies and approaches have been performed with a few outstanding examples, such as those of Ruan et al.; Cepeda et al.; Lu et al.; and Sanghani et al., in whose studies based on conventional MRI sequences and ML algorithms, accurate prognostic classification exceeded 90% [29,52,55,56]. Moreover, advanced MRI sequences can also be employed for prognostic purposes. Thus, some authors have implemented functional resting-state MRI and DTI (Diffusion Tensor Imaging) studies to build structural and connectivity networks, extract features and process them with ML and DL algorithms [19,50,59].

An interesting conceptual approach was implemented by Lee et al., who used relative texture features from perfusion maps to predict the survival status at 12 months [22]. Features extracted from enhancing and nonenhancing regions of the tumor were computed to provide these relative features. In addition, kinetic features calculated from the gadolinium concentration time-series of perfusion data in both regions were also extracted [22]. Nonetheless, relative texture features displayed a higher impact on prognosis than kinetic features [22].

Delta-radiomics, which consists of features extracted at different time points, provides information about how radiomic features change over time. In a small cohort, Chang et al. demonstrated the strong potential of delta-radiomics combined with a DL algorithm [39]. It is still unknown which time lapes might be more informative depending on the studied outcome variable. Regardless, delta features seem to provide higher predictive information than one-time features, which makes it even more logical for survival prognosis.
Figure 2. (A) Diagram depicting an example of the conventional process for studies implementing radiomics and machine learning algorithms. (B) Diagram of an example of a survival prediction investigation based on deep learning.

ML methods may also generate different radiomic profiles of gliomas that could potentially translate their underlying biological features. Itakura et al. and Rathore et al. classified gliomas into three clusters with different survival prognoses using different methodologies [60,61]. Remarkably, both teams reported three different radiomic profiles that actually shared some characteristics [9]. Specifically, rim-enhancing subtypes granted better prognosis in both reports. Indeed, tumor subgroups were associated with molecular subtypes, location and genetic mutations [60,61]. These findings, which require further validation, support the idea of radiomics as a virtual biopsy, turning the corner to more personalized and precise communication with patients and relatives.

Deep learning, as a branch of AI and considered a fully machine learning method able to train on its own without human intervention, has consistently defeated rivals in image recognition competitions such as ImageNet. The increasing amount, complexity, types and availability of data partially explains the swift direction towards DL for medical applications, as DL does not strictly require a human-driven refining of data. Moradman et al. demonstrated the superior ability of DL to establish complex correlations between multiple clinical, biological and therapeutic variables, and survival in patients diagnosed with glioblastoma [11]. A feed-forward NN offered higher accuracy on survival prognosis than the random survival forest and Cox proportional hazard regression models [11].

Obliviating the tasks that texture analysis involves, Ben Ahmed et al. built a convolutional NN based on MRI snapshots that outperformed the accuracy of the best-known predictor by 6% [14]. Using nonlabelled, nonsegmented snapshots offers a fast and low-cost...
way to feed a DL algorithm [14]. Nonetheless, DL might also be used as a method to mine images. With a hybrid approach, Nie et al. applied a DL method to automatically extract features that would otherwise be difficult to design [34]. These DL features together with key demographic and tumor-related features allowed us to stratify patients into long and short survival groups through an SVM classifier with 90.5% accuracy [34]. DL also supports the inclusion of advanced MRI sequences, as demonstrated by Yan et al., who compared a clinical nomogram with a DL signature based on DTI data [62]. Yan et al. obtained better results with the DL signature, achieving a C-index of 0.9 on an external validation dataset [62]. In addition, the authors suggested the existence of an association of DL features with biological pathways involved in glioma development (synaptic transmission, activation of AMPA receptors, axon guidance, calcium transport, etc.) [62].

4.1. Future Challenges

4.1.1. Data Availability

AI training requires a large, high-quality dataset to build robust algorithms. Creating such datasets is costly and time consuming and demands that professionals shift from care provision to data production. This burden is especially problematic in rare diseases such as GBM. Therefore, a culture of data sharing is needed. Cooperative efforts, such as The Cancer Imaging Archive or the Ivy Glioblastoma Atlas project, have contributed to increasing data availability. Additionally, data could be improved by the harmonization of image acquisition protocols across institutions. Automatic data acquisition, often used by AI in other fields, clashes with the need to preserve the confidentiality of medical data [63].

4.1.2. Opening the Black Box

AI algorithms are built from associations that are not fully disclosed by the algorithm itself. Therefore, drawing conclusions between radiomic features and glioma characteristics might be misleading since their relationships are unknown, and predictive models might be based on variables derived from similar features that might be overrepresented [64]. Indeed, understanding the underlying mechanisms by which biology translates into radiomic features is a classic concern and matter of current investigations. Nonetheless, recent advances, such as principal component analysis and saliency maps, have relieved these concerns by unveiling part of the structure of AI algorithms [65]. Radiomic features might be the fine manifestation of molecular phenotypes in grayscale images [20].

4.1.3. Humanizing AI

When AI is implemented to fulfil a given task, human vs. machine approaches are often used to elucidate who can better perform it. Modern AI applications to the medical field have suggested the benefits of human-in-the-loop strategies to overcome the unique challenges medicine poses to AI. In expert augmented machine learning, researchers combined the knowledge of experts to solve specific problems where AI algorithms might fail the most [66]. Thus, the quality of training data might be notably improved by integrating the information that specialists base their decisions on. Similarly, in active learning, key data are obtained from the expert by the algorithm itself to increase the quality of the training dataset or enhance the ability of the algorithm to extract useful information [67,68].

4.1.4. Integrating AI into Clinical Practice

The ultimate goal of research in medicine is transferring the lessons learned in the laboratory to clinical practice. The topic covered in this review is not an exception. The reports presented herein are commendable efforts to find key features and methods to improve patients’ prognostic estimation. However, the methodology that most of these investigations involve is extremely time-consuming and makes it inefficient for daily implementation in a clinical context. The next paramount advancement in this field, beyond increasing accuracy or simplifying the workflow, will be the production of an open
source, easily integrable and precise AI algorithm that requires simple or null intervention of the physician for prognostic estimation from multimodal MRI studies.

4.2. Limitations

The major limitations of previous publications can be summarized in the following sections:

1. Patient selection: In most published articles, patients were included without considering the extent of resection, which is one of the main factors associated with overall survival. Therefore, if the intention is to use the imaging characteristics independently to predict the outcome, it is necessary either to include only patients with gross total resection or perhaps to introduce in the model a variable through which the degree of resectability of the tumor can be quantified [55].

2. Image preprocessing and data extraction: There is significant variability in the methods employed to preprocess MRI images and in the parameters used to extract radiomic features. This pitfall explains the differences in the results obtained on the same patient dataset (such as the TCIA patient cohort) [47,49]. Therefore, the lack of details about the preprocessing pipeline used by the different authors limits the reproducibility of their results [11,35,44,54].

3. Classification task vs. survival regression: There are discrepancies in how different authors approach the challenge of predicting survival in GBM. On the one hand, some studies attempt to carry out a survival analysis, in which the relationship between the radiomic variables and survival in days is expressed by the Harrell index or the hazard ratio [6,18,35,37]. On the other hand, there are works in which a classification task has been carried out to create survival groups. The latter methodology is much easier to interpret and has a clinical orientation [6,19,23]. However, the cut-off point for establishing survival groups is entirely arbitrary in various publications [19]. For example, it does not seem helpful to define a short-term survivor as one who does not exceed ten months of life when the overall median survival is 15 months. Therefore, unifying the criteria for short- and long-term survival definitions in this neoplasm is essential.

4. Lack of validation in multi-institutional data: Although there are studies with promising results, the lack of validation in a multicenter cohort seriously limits the application of predictions in a clinical setting [55]. One of the challenges of models based on radiomic features is to find a set of stable and reproducible features so that they can be used regardless of artifacts produced during image acquisition, MRI acquisition protocols, and scanner manufacturers.

5. Conclusions

Advanced image analysis and data processing methods have gained momentum over the last decade. Methods such as radiomics, texture analysis, ML and DL have been successfully implemented to provide an accurate survival estimation and risk factor identification for patients diagnosed with GBM. The wide variety of available approaches prevents unifying methods and drawing consistent conclusions from reported results. However, despite its limitations, the existing symbiosis between radiomics and AI represents a robust approach to build evidence and address unanswered questions in neuro-oncology. In fact, AI is no longer a matter of future but a living, vibrant and powerful reality.

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