REVIEW

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A review on the applications of artificial intelligence and big data for glioblastoma multiforme management

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Abstract

Glioblastoma is known as an aggressive type of brain tumor with a very poor survival rate and resistance to different treatment methods. Considering the difficulties in studying glioblastoma, the development of alternative methods for the identification of prognostic factors in this disease seems necessary. Noteworthy, imaging, pathologic, and molecular data obtained from patients are highly valuable because of their potential for this purpose. Artificial intelligence (AI) has emerged as a powerful tool to perform highly accurate analyses and extract more detailed information from available patient data. AI is usually used for the development of prediction models for prognosis, response/resistance to treatments, and subtype identification in cancers. Today, the number of AI-aided developed algorithms is increasing in the field of glioblastoma. Challenges in the diagnosis of tumors using imaging data, prediction of genetic alterations, and prediction of overall survival are among the most popular studies related to glioblastoma. Hereby, we reviewed peer-reviewed articles in which AI methods were used for various targets in glioblastoma. Reviewing the published articles showed that the use of clinical imaging data is reasonably more popular than other assessments because of its noninvasive nature. However, the use of molecular assessments is becoming extended in this disease. In this regard, we summarized the developed algorithms and their applications for the diagnosis and prognosis of glioblastoma tumors. We also considered the accuracy rates of algorithms to shed light on the advancements of different methodologies in the included studies.

Keywords Glioblastoma multiforme, Artificial intelligence, Deep learning, Radiomics, Genomics, Precision medicine

Background

Glioblastoma grade IV, formerly called glioblastoma multiforme (GBM), is known as the most aggressive brain tumor with a survival of less than two years [1]. The prevalence of glioblastoma is approximately 3.2 in 100,000 population, while it has the highest mortality rate of 90% in 5 years among all the forms of brain tumors [2, 3]. Glioblastomas are divided into two subgroups based on their origination including primary tumors which originate from brain tissue, and secondary tumors which are developed via metastasis from other tissues and compose 10–45% of glioblastomas [4]. The median age of glioblastoma diagnosis is 65 years, and it has been found that the probability of incidence for this disease in males is higher

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than in females. Based on the classification of WHO in 2021, glioblastoma is pathologically diagnosed with IDH wild type and mutations in *TERT* promoter, chromosomes 7/10, *EGFR* gene [5]. In addition, the genomic drivers of glioblastoma include amplification of PDGFRA and MET, deletions in CDK2A/B, and gain mutations of NF1, TET2, DNMT3Am and LTBP4 [6–8]. On the other hand, genomic changes in DNA mismatch repair genes such as MSH1, MSH2, etc., and altered gene expression in endothelial marker genes and extracellular-associated genes are among the molecular hallmarks of glioblastoma [9].

Artificial intelligence (AI) is a set of continuous activities in which technology performs smart behaviors without human direct intervention. Amisha et al. described AI as the science of engineering for the smart machines production in 1965 [10]. AI is increasingly used in medical sciences for various targets including improvement of decision-making in diagnosis, prognosis, and treatment of diseases [11]. It is also poised to broadly reshape medicine and improve the experiences of both clinicians and patients. Machine learning (ML) algorithms such as K-nearest neighbor (KNN), random forest (RF), support vector machine (SVM), and logistic regression (LR) are used in various medical fields. For example, a large number of studies have been conducted in the oncology field in order to find prognostic factors, improve diagnostic methods, and predict response to treatments based on the genetic factors. In addition, using the deep learning (DL) approach, it is possible to study cancer signaling systems in a large-scale data-driven fashion [10]. Accordingly, these methods lead to faster and better decision-making processes by physicians [12–15]. In addition, AI is also exploitable physically in medical sciences by which robots and medical devices are developed to assist nurses, doctors, and surgeons [16].

Despite the advancements of AI in medical sciences and brain tumors, several of concerns remain to be answered. The accuracy of predictions made by ML/DL algorithms, the benefits of designed algorithms for improvement of brain tumor classification, and prediction of response to treatment for this disease can be mentioned as the main concerns. In this review, we searched for the relevant studies using keywords including "glioblastoma," "GBM," "machine learning" (ML), "deep learning," and "artificial intelligence" in databases of PubMed, Embase, and Web of Science. Hereby, we summarize applications of virtual artificial intelligence for glioblastoma in various fields such as the use of radiomics for diagnosis and prognosis, and molecular studies for prediction of response to treatment and its benefits for designing personalized treatment methods.

Radiomics and AI applications for glioblastoma

The pathological and molecular assessments of tumor biopsies are the reference standard for tumor diagnosis and grading. However, a noninvasive tool capable of accurately classifying tumor subtypes and inferring its grade would be highly desirable. There are several non-invasive imaging techniques which help to visualize glioma tumors. Computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) are important diagnostic tools used for decision-making about the standard care of glioblastoma in clinical practice. MRI includes detailed data of the lesion location, size, extent, features, tumor and surrounding environment relationship, and associated mass effect. Beyond structural information, MRI can also assess microstructural features such as lesion cellularity, microvascular architecture, and perfusion. Conventional radiomic programs can generally analyze medical images, but they are not accurate enough for analysis of detailed aspects of images. Advanced imaging techniques may demonstrate more details of brain tumors related to their heterogeneity, aggressiveness, and grade; however, they are limited in assessing the microscopic changes that cause macroscopic ones. Convolutional neural network (CNN) from deep learning (DL) algorithms with several applications in image classification and image segmentations are widely used in brain tumor classification [12, 17]. In turn, deep learning, a subcategory of machine learning, is a network model constructed from features of input data which are connected to output layer via several intermediary layers. DL provides automatic learning of features and their representation in a hierarchical manner at various levels. These characteristics have made DL a robust technique for feature extraction and data modeling processes. The initial layers perform simple processing of input data or learn the easy features, while the upper layers perform complex features learning and lead to the results more precisely. Therefore, DL is suitable for dealing with large and complex data [18, 19].

Prediction of survival for patients with an aggressive tumor such as glioblastoma helps oncologists and surgeons to design treatment protocols appropriately for patients. Punctual preoperative prognosis holds great importance for the personal treatment of glioblastoma patients. DL performs multi-faceted MRI image analysis and accordingly assists specialists in predicting the OS time for these patients. The classification and recognition of glioblastoma tumors using MRI is a crucial process before surgery. In addition, the assessment of tumor location, composition, and extent of tumors are of high importance. On the other hand, manual tumor classification is a time-consuming and error-prone process. In this regard, Eijgelaar et al. designed an algorithm using

DL (sparsified algorithm) which can be used to analyze data in a generalized and specific manner. Consequently, glioblastoma tumors are classified automatically, which it significantly assists physicians in accomplishing better surgeries in a shorter time [20] (Fig. 1).

Lao et al. used a radiomic model that could predict patient OS by searching the intricate details of medical images. Interestingly, this program can play a crucial role in treating individuals with glioblastoma by categorizing them into high-risk and low-risk groups [21]. Biophysical modeling can provide more complex and extensive aspects of glioblastoma tumor growth. In this regard, Pati et al. designed a linear regression (LR) model based on DL that utilizes three components: diffusion coefficient in white matter, mass parameter, and estimated days of tumor growth based on the patient's conditions. This algorithm notably facilitates tumor growth estimation for physicians [22]. In addition, glioblastoma primary and metastatic tumors often overlap in MRI images, and consequently, their diagnosis becomes challenging for radiologists. Shin et al. developed a DL-based model that effectively distinguishes between these two types of images with high-level accuracy [23]. In addition, glioblastoma and primary central nervous system lymphoma (PCNSL) are recognized as primary brain tumors. These

tumors exhibit significant similarities in MRI images. Considering that these two tumors have different treatment methods, the development of an accurate diagnosis method using MRI data is undoubtedly important. Xia et al. introduced a model based on the CNN algorithm that easily elucidates the differences between the MRIs of these two tumor types [24]. Another issue is separation between glioblastoma and brain metastases which remains as an issue in medical imaging. Physicians should be able to accurately differentiate between these two tumor types. Bea et al. presented a CNN model that uses radiomic features to easily distinguish between the mentioned two tumor types [25]. Tumefactive demyelinating lesion (TDL) and PCNSL are common intracranial neuroepithelial lesions in glioblastoma. These regions can be observed as solitary or scattered forms. In solitary form, they are seen as well-defined units with surrounding edema. In scattered form, they appear as irregular scattered masses. Although these tumors have different origins, they show relatively intersections in MRI images. Researchers increased the accuracy of diagnosis of scattered forms by a large number of MRI data and using DL algorithms. This approach also facilitated the process of separating these brain lesions in MRI images. Consequently, it helps physicians to make better decisions in
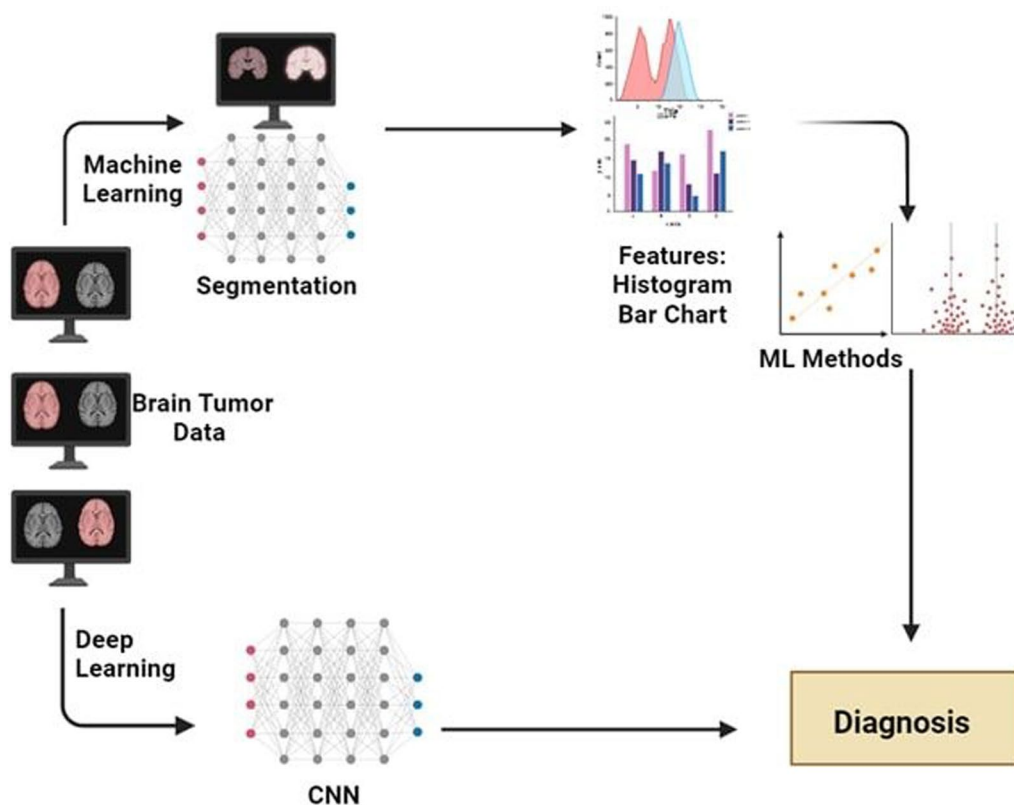

Fig. 1 Machine learning and deep learning in brain tumor detection

the management of patient treatment [13]. Preoperative multimodal imaging data has been used to predict the OS of patients via extraction of genotype-related features from MRI data [26]. CNN algorithm can accurately classify glioblastoma tumors, which is based on a nifty net framework at the same time. Additionally, CNN algorithms are very helpful in the differentiation between glioblastoma and secondary brain tumors in MRI images [20]. Tumor cells of glioblastoma have a highly invasive phenotype. As a result, there is a 90% chance of tumor recurrence that is very prevalent even after complete resection and performing chemotherapy and other cancer treatments in the tumor area. Also, recurrences usually occur at the site of tumor removal or in areas near the tumor site. Yan et al. recognized the non-enhanced peritumoral region by utilizing the CNN algorithm and MRI data, which helped determining probable regions of glioblastoma cell progression in the future [27] (Table 1).

Another research indicated that unsupervised DL such as DBN algorithms with layer models works great for glioblastoma subtype recognition [28]. A designed radiometric model operates based on DL algorithms and shows successful application in finding deep aspects and details of MRI images. In addition, in this model, researchers employ COX regression which leads to precise prediction of OS in glioblastoma patients [21]. Another ML algorithm, called as deep neural network (DNN), supports specialists in discriminating glioblastoma and brain secondary tumors using only imaging data [23]. DL algorithms are also able to diagnose mutated genes that lead to glioblastoma appearance and OS prediction [29]. Researchers claimed that ML algorithms such as LR, SVM, k-nearest neighbor (KNN), and naïve Bayes (NB) are applied for glioblastoma tumor classification; however, the CNN algorithm assists this tumor categorization as well [25, 30] (Fig. 2).

Genomics, precision medicine, and AI applications for glioblastoma

Precision oncology is fed by data extracted from high throughput sequencing (HTS) techniques and is progressing toward flexible treatment methods based on the personal genome diversities. HTS techniques, including next-generation sequencing (NGS), provide a robust resource for the identification of targeted therapy triggers and risk factors for cancers. Integration of NGS data with imaging and clinical data via AI methods leads to various predictions about personal sensitivities, susceptibilities, and responses to treatment precisely. In addition to the mentioned general applications, the use of AI in cancer big data analytics has technical advantages such as scaling up the data processing and accurate predictions where clinicians may have different diagnostics

and decisions about treatments [52–54]. Thang et al. designed a multi-task CNN that efficiently considered the tumor genotype in predicting OS of patients and it yielded an accurate predictive algorithm [26]. In cancerous cells such as glioblastoma, there are several signaling pathways that are initiated via mutated genes. This signaling pathway may conduct abnormal functionalities in these cells. Analyzing these processes can potentially lead to the development of personalized cancer treatment approaches. In this regard, the DBN algorithm was introduced by Young et al. which examines glioblastoma tumors using genomic data, and these processes considerably help in understanding the underlying mechanisms of tumor subtypes [28]. In this regard, there is a group of mutated genes involved in the development of glioblastoma. DL- and ML-based models can analyze and identify these genes, which result in effective prediction of OS for patients with this type of tumor. This algorithm also helps physicians to make effective decisions for selecting better treatment methods based on the high-risk/low-risk categorization [29]. Molecular features of glioblastoma cells have always been a challenge for medical scientists, but AI has provided valuable assistance in this area. Munquad et al. utilized SVM, LR, and RF algorithms for classification of glioma cells based on molecular variables and gene expression profiles [30] (Fig. 3).

Challenges and future prospective

Gliomas are a heterogeneous group of common intracranial tumors that cause significant mortality and morbidity. Gliomas are classified into four grades (I to IV) of increasingly aggressive malignancy and worsening prognosis. Indeed, in clinical practice, tumor type and grade influence treatment choice. According to the World Health Organization (WHO) Grade IV tumors, so-called glioblastoma the most aggressive primary brain tumor, with a median survival after diagnosis of just 12–15 months. Applications of AI for this disease in different aspects have also disadvantages. Malfunctioning in designed algorithms or processors along with lack of accurate results or incorrect interpretations of the results can lead to the wrong conclusions and subsequently to wrong decision-making for physicians [55]. On the other hand, overfitting is the main problem for predicting various aspects of glioblastoma diagnosis, prognosis, and treatment which warns physicians to not completely rely on AI-based applications and also leads specialists in medical-AI to develop more accurate and reliable software. For this purpose, a vast amount of data is not only required for training, testing and internal validation, but also for external validation of algorithms. Noteworthy, the use of algorithms for prognosis can be confusing, since the results change based on the slight changes

Table 1 Application of radiomics in GBM

Author	Year	Prediction		Method	Accuracy
Faghani et al. [31]	2023	MGMT promoter methylation	T2W1	CNN: whole brain, Slice-wise, Voxel-wise	65.42%, 61.37%, 56.84%
Zhang et al. [32]	2023	TERT promoter mutation	T1CE, T1W1, T2W1	CNN	99%
Pasquini et al. [33]	2021	IDH-mutant and IDH-wild GBM	T1, T2, FLAIR, MPRAGE, rCBV	CNN	77%, 77%, 67%, 66%, 83%
Zhang et al. [34]	2023	TERT mutation	T1WI	CNN	82.3%
Saxena et al. [35]	2023	MGMT genotype prediction	T1, T2, FLAIR, T1GD	SVM, XGBOOST, KNN, RF, LightGBM	75.3%
Jaruenpunyasak et al. [36]	2023	Primary CNS Lymphoma versus corpus callosal tumor	T1-weighted	DL+Regression regularization DL+drop-out regularization	83% 84%
Bathla et al. [37]	2023	Differentiation of GBM, IMD, and PCNSL	T1W, T2W, FLAIR, DWI, T1CE	CNN	85.4%
Liu et al. [38]	2021	Distinguish GBM from Brain Metastasis	T1WI, T2WI, T1CE	CNN	86% 76% 93%
Shoushtari et al. [39]	2022	MRI image segmentation	T1CE, FLAIR	DeepNet	97.53%
Rui et al. [40]	2023	Brain tumor grading and molecular subtyping	T2-FLAIR, T1W1	CNN	74%
Chang et al. [41]	2019	Tumor volume	FLAIR	DL	91.7%
Ermis et al. [42]	2020	Brain resection	T1W, T2W, FLAIR	DL	86%
Ramesh et al. [43]	2023	Brain tumor segmentation	T1W, T2W, FLAIR	DL	73%
Du et al. [44]	2023	Recurrence of GBM	MRI, TERT mutation, KPS	LASSO	85%
Moassefi et al. [45]	2022	True progression and pseudo-progression	T1, T2-weighted	DL	76.4%
Chiu et al. [46]	2021	GBM tumor subregions classification	T1CE, T2W, T2-FLAIR	DL	90.4%
Meaney et al. [47]	2023	Estimation of tumor cell diffusivity and proliferation rate	MRI	DL	NA
Kazerooni et al. [48]	2022	Prediction of survival	Radiomics, Genomics, and clinical measures	SVM	75%
Li et al. [49]	2020	Detecting Pseudotumor progression after GBM therapy	MRI	SVM	92%
Acbari et al. [50]	2020	Identifying Tumor progression in GBM patients	MRI	DL	84%
Bacchi et al. [51]	2019	Determining high-grade glioma progression	MRI	DL, CNN	73%

TERT: telomerase reverse transcriptase, FLAIR: fluid-attenuated inversion recovery, MGMT: O(6)-methylguanine-DNA methyltransferase, DL: deep learning, CNN: convolutional neural Network, MPRAGE: Magnetization Prepared—RApid Gradient Echo, rCBV: Relative cerebral blood volume, IMD: intracranial metastatic disease, PCNSL: primary CNS lymphoma, DeepNet: Deep Network Training

in the included variables [56]. Accordingly, achieving the accurate results and best features for prediction of outcomes in each stage of disease and for every application including prognosis, diagnosis, and treatment and their subgroups seems necessary. In this regard, the determination of the most effective variables for each application

will help to not only use a limited number of variables, but also to develop more accurate algorithms. An aggressive type of cancer such as glioblastoma has still a wide area of unclarities around the prognosis of patients and categorizing them to low risk and high risk, while in the diagnosis of glioblastoma and its subtypes based on the
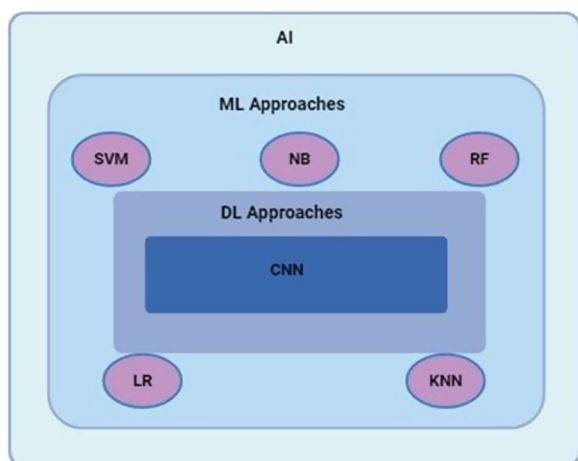
Fig. 2 The overview of AI-based GBM management methods

pathobiology results and synchronizing these results with imaging results to develop noninvasive AI algorithms, it is important to consider that there are already conflicts between genome profiling of mutations for grading tumors and imaging-based diagnosis. Decision-making about treatment methods for glioblastoma patients is an ongoing concern. Glioblastoma treatment includes standard care including surgical removal, chemotherapy, and radiotherapy. However, according to the genomic variations in patients, different resistance types to standard care and novel treatments such as immunotherapies are observed in glioblastoma patients [57, 58]. Also, the lack of standardized radiomics parameters and data can induce some challenges in the generalization of ML algorithms, which have limited AI model efficiencies in detecting high-grade gliomas and predicting patient survival [59]. Although AI models are beneficial for helping GBM patients, medical data quality and paucity, AI methods transparency, different image imputations, and ethical problems linger as the concerns [60, 61]. As it was mentioned above, there are still lots of questions regarding glioblastoma which can be answered using genomics data such as prediction of response to treatment rate, resistance to treatment, recurrent cases, and survival rate. In this regard, AI algorithms are required in order to predict resistance to each treatment type based on the molecular profiling. These algorithms will help to save time in treating patients especially those who are at high risk and design an effective treatment pathway which can be most effective and lead to longer survival in GBM patients.

Conclusion

Glioblastoma is known for low survival and short lifetime of the patients. Considering lots of uncertainties around the diagnosis and prognosis of the patients
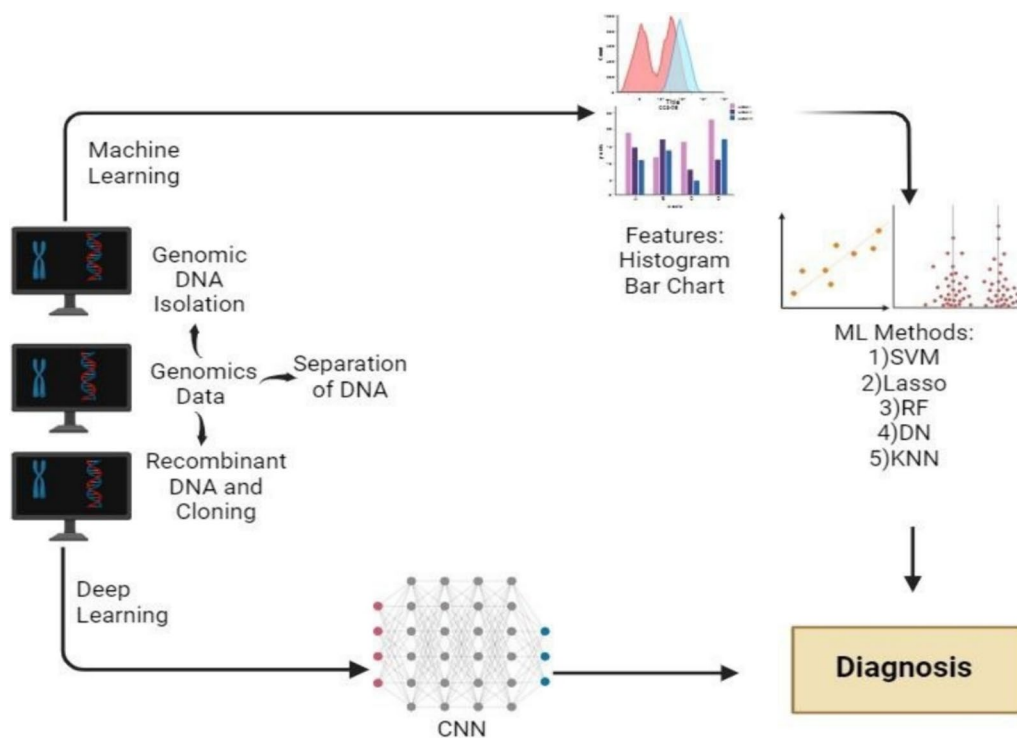

Fig. 3 Machine learning and deep learning in genomic data and diagnosis

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and decision-making for the most effective treatment approach, AI can help to resolve these issues. Development of verified and reliable applications with the lowest overfitting, underfitting, false-positive ratio, and false-negative ratios is required to boost progress toward improving the management of glioblastoma patients. In this regard, the identification of the most effective variables for each application is necessary. In total, AI has shown the ability to create a brighter future for physicians in glioblastoma disease management, especially in estimating patient OS and other tumor-related complex information with radiomics and molecular assessment tools, which needs the contribution of physicians and computer scientists.

Abbreviations

AI	Artificial intelligence
ANN	Artificial neural network
CNN	Convolutional neural network
CT	Computed tomography
DNN	Deep neural network
DL	Deep learning
GBM	Glioblastoma multiforme
HTS	High throughput sequencing
KNN	K-nearest neighbor
LR	Logistic regression
LR	Linear regression
ML	Machine learning
MRI	Magnetic resonance imaging
NB	Naïve Bayes
NGS	Next-generation sequencing
OS	Overall survival
PCNSL	Primary central nervous system lymphoma
PET	Positron emission tomography
RF	Random forest
SVM	Support vector machine
TDL	Tumefactive demyelinating lesion
WHO	World Health Organization

Declarations

Ethics approval and consent to participate
Not applicated.

Consent for publication
Not applicated.

Availability of data and materials
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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