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Improving Glioblastoma Multiforme Recurrence Prediction through Integrated Radiomics and Deep Learning Techniques

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Abstract:

Glioblastoma multiforme (GBM) is one of the most lethal forms of brain cancer, with a five-year survival rate of only 4% to 5%. The recurrence rate is alarmingly high, reaching up to 90%. While tumor-treating fields have shown potential in extending survival, their efficacy in treating recurrent GBM remains limited. This study aims to leverage Deep Learning (DNN) to predict the recurrence of GBM in patients, both pre- and post-surgery. Utilizing advanced computational techniques, this research employs radiomics to analyze brain tumor images, aiding clinicians in identifying tumor spread, predicting post-surgical recurrence, and estimating patient survival. Pre-surgery, Multi-Parametric Magnetic Resonance Imaging (MP-MRI) scans are used to detect tumor locations and forecast potential recurrences. To enhance image processing, Z-score normalization and spatial resampling are applied. Additionally, a model was developed to address the issue of imbalanced data in medical imaging. The study utilized Contrast-Enhanced T1-Weighted Imaging (CE-T1WI) MRI to assess treatment effectiveness and predict recurrence-free survival. A Deep Neural Network was trained to forecast tumor recurrence, identifying patients at risk of early recurrence. Feature extraction from brain images was performed using the Inheritable Bi-Objective Combinatorial Genetic Algorithm. The accuracy of the recurrence predictions was validated and compared against other models, including CNN Inception-V3, CNN AlexNet, and VGG16, using the Python programming language. Results indicate that the proposed method surpasses existing techniques by 3%, 4%, and 5% in accuracy, specificity, and sensitivity, respectively. This research demonstrates that in a retrospective patient population, predictions of patient survival and time to recurrence exhibit high sensitivity, specificity, and accuracy, offering a promising tool for improving GBM management and patient outcomes.

Keywords: Glioblastoma multiforme (GBM), Deep Learning (DNN), Radiomics, Multi-Parametric Magnetic Resonance Imaging (MP-MRI), Tumor recurrence prediction, Inheritable Bi-Objective Combinatorial Genetic Algorithm.

1. Introduction

Glioblastoma multiforme (GBM) is recognized as one of the most aggressive and lethal forms of brain cancer. Characterized by rapid progression and a high degree of invasiveness, GBM poses

significant challenges to effective treatment and management. The prognosis for GBM patients remains dire, with a five-year survival rate of only 4% to 5%. The recurrence rate for GBM is alarmingly high, reaching up to 90%, which complicates treatment strategies and diminishes the quality of life for affected individuals[1]–[3]. Despite advancements in therapeutic interventions, including tumor-treating fields and other innovative approaches, the management of recurrent GBM remains a formidable challenge. These treatments, although beneficial in extending overall survival, often fall short in effectively addressing tumor recurrence[4], [5].

In recent years, the advent of machine learning (ML) and deep learning (DL) technologies has transformed the landscape of medical imaging and diagnostics. These technologies offer promising avenues for improving the accuracy and efficiency of disease detection, prognosis, and treatment planning. Radiomics, in particular, has emerged as a powerful approach for extracting quantitative features from medical images, providing valuable insights into tumor characteristics that are not discernible through traditional imaging techniques. Multi-Parametric Magnetic Resonance Imaging (MP-MRI) has proven instrumental in this regard, enabling the detailed analysis of tumor properties and potential recurrence sites[6], [7].

Despite these advancements, several critical gaps remain in the current body of research. Existing studies predominantly focus on tumor classification and overall survival prediction rather than explicitly addressing the challenge of recurrence prediction. Additionally, the issue of imbalanced data in medical imaging datasets has not been adequately tackled, leading to potential biases and compromised model performance. The utilization of advanced feature extraction algorithms, such as the Inheritable Bi-Objective Combinatorial Genetic Algorithm (IBCGA), in the context of GBM recurrence prediction is still in its nascent stages. Moreover, there is a lack of comprehensive comparative analyses of various DL architectures, including CNN Inception-V3, CNN AlexNet, and VGG16, specifically tailored for GBM recurrence prediction[8]–[10].

This study aims to bridge these research gaps by proposing a novel DL-based framework designed explicitly for predicting GBM recurrence. Our approach leverages the strengths of radiomics and MP-MRI to extract detailed tumor features and address the challenge of imbalanced data. We employ advanced feature extraction methods, including IBCGA, to enhance the predictive power of our model. Additionally, we conduct a rigorous comparative analysis of several state-of-the-art DL architectures, such as CNN Inception-V3, CNN AlexNet, and VGG16, to identify the most effective model for this specific application. Our contributions are threefold:

i. We develop a robust DL-based framework that integrates radiomic features and MP-MRI data to predict GBM recurrence with high accuracy.
ii. We address the issue of imbalanced data through the implementation of novel data normalization and resampling techniques.
iii. We provide a comprehensive evaluation of various DL architectures, offering valuable insights into their relative performance in the context of GBM recurrence prediction.

By addressing these key areas, our study aims to enhance the clinical management of GBM, providing clinicians with a powerful tool for early detection and intervention, ultimately improving patient outcomes and survival rates.

2. Analysis of existing research

Recognized as one of the most aggressive and fatal types of brain cancer, glioblastoma multiforme (GBM) has a pitiful five-year survival rate of just 4% to 5%. Nearing 90% of recurrences make things more difficult for both patients and medical professionals. Though tumor-treating fields are one of the treatment modalities that has advanced, efficient management of recurrent GBM is still elusive. This emphasizes how urgently novel methods to tumor recurrence prediction are needed. These methods could greatly improve clinical results by allowing for timely and customized therapeutic interventions.

Machine learning (ML) and deep learning (DL) techniques have transformed many aspects of medical imaging and diagnosis in recent years[11], [12]. Extraction of quantitative features from medical images, or radiomics, has become a potent tool for improving imaging-based diagnostics' predictive accuracy. Tumor features and possible recurrence sites have been especially well identified by Multi-Parametric Magnetic Resonance Imaging (MP-MRI). Understudied as shown in table-1 is the integration of these cutting-edge methods into a coherent framework for GBM recurrence prediction both before and after surgery.

Table 1 Major existing research analysis

Author	Dataset	Method	Methodology	Key Finding	Results	Recurrence Prediction
G. Bathla et al.[13]	Multi-institutional dataset	Machine Learning and Deep Learning	Comparison of ML and DL methods for classifying malignant tumors in neuro-oncology	AI methods can effectively classify different malignant tumors	Improved classification accuracy across multiple institutions	Yes
S. Cepeda et al.[14]	Intraoperative ultrasound B-mode and strain elastography	Deep Learning	Automated DL approach for differentiating glioblastomas from solitary brain metastases using ultrasound	DL can differentiate between glioblastomas and brain metastases with high accuracy	Enhanced differentiation capabilities using intraoperative ultrasound data	Yes
L. Chato et al.[15]	Glioblastoma patient data	Machine Learning and Radiomics	Predicting overall survival time for glioblastoma patients using ML and radiomic features	Radiomic features are significant predictors of overall survival time	Accurate prediction of overall survival time for glioblastoma patients	No
A. de Causans et al.[16]	Post-contrast 3D T1-weighted MR images	Machine Learning	Development of an ML classifier to distinguish glioblastoma from solitary brain metastasis	Radiomic features from post-contrast MR images can accurately distinguish between tumor types	High classification accuracy in distinguishing glioblastoma from solitary brain metastasis	Yes
F. Dong et	Contrast-	Decision	Differentiation	Quantitative	Decision tree	No

al.[17]	enhanced MRI data	Tree	between pilocytic astrocytoma and glioblastoma using radiomic features	radiomic features can effectively differentiate between the two types of tumors	model achieved high accuracy in differentiation using radiomic features	
E. Ermiş et al.[18]	Brain resection cavity images	Deep Learning	Fully automated brain resection cavity delineation for radiation target volume definition	DL can automate the delineation of brain resection cavities for radiation therapy planning	Improved delineation accuracy for radiation therapy target volumes	No
A.-J. Fordham et al.[19]	Advanced imaging modalities for brain tumors	Various Imaging Modalities	Review of current literature on differentiating glioblastomas from solitary brain metastases	Advanced imaging modalities provide significant insights for differentiation	Summarized advancements in imaging techniques for tumor differentiation	Yes
J. Fu et al.[20]	Preoperative multimodal MR images	Deep Learning	Workflow for glioblastoma survival prediction using preoperative MR images	DL-based workflow can predict survival with high feasibility using preoperative imaging data	High feasibility of predicting survival using preoperative MR images	No
G. Lu et al.	CT-based imaging data	Machine Learning and Deep Learning	Predicting primary CNS lymphoma and glioma types using ML and DL models	ML and DL models can predict different types of CNS tumors with high accuracy	High prediction accuracy for CNS tumor types using CT-based models	No
Z. R. Samani et al.[21]	Peritumoral microenvironment images	Deep Learning	Characterization of tumor signatures using DL for peritumoral microenvironment analysis	DL-based characterization provides distinct tumor signatures for glioblastomas and brain metastases	Enhanced characterization of the peritumoral microenvironment using DL	Yes
N. C. Swinburne et al.[22]	MRI advanced imaging data	Machine Learning	Semi-automated classification of glioblastoma, brain metastasis, and CNS lymphoma	ML can semi-automate the classification of different brain tumors using advanced	Improved semi-automated classification accuracy for various brain tumors	No

				imaging data		
L. Tariciotti et al.[23]	Preoperative imaging data	Deep Learning	Differentiation of glioblastoma, brain metastasis, and CNS lymphoma using DL models	DL models can effectively differentiate between different types of brain tumors preoperatively	High differentiation accuracy using DL models for preoperative imaging	Yes
D. S. Wankhede et al.[24]	Glioblastoma patient survival data	Deep Learning	Dynamic architecture-based DL approach for predicting glioblastoma survival	DL can predict survival time for glioblastoma patients with high accuracy using dynamic architectures	High survival prediction accuracy using dynamic DL architectures	No

Though encouraging, the studies now in progress highlight a number of drawbacks. Recurrence prediction is not explicitly addressed by most of the models now in use; instead, they concentrate on classification or survival prediction. Furthermore, there are possible biases and lower model efficacy because the issue of imbalanced data in medical imaging has not received enough attention. Rarely are feature extraction algorithms like the Inheritable Bi-Objective Combinatorial Genetic Algorithm (IBCGA) applied in this setting. Moreover, thorough comparison studies of several DL architectures for recurrence prediction, such as CNN Inception-V3, CNN AlexNet, and VGG16, are lacking.
These gaps are intended to be filled by this work, which proposes a strong DL-based framework that uses sophisticated radiomic features and addresses data imbalance problems to predict GBM recurrence. Modern feature extraction techniques are used in this work, which is then rigorously validated against existing models to provide a very accurate and clinically useful tool for managing GBM. The suggested method not only seeks to increase prediction accuracy but also provides a scalable solution that can be included into current clinical processes, so improving patient outcomes by means of prompt and accurate therapeutic actions.

3. Proposed approach

Glioblastoma multiforme (GBM) is a highly aggressive grade IV brain tumor with a limited overall survival rate. Precise therapy planning for recurrent GBM tumors heavily relies on understanding the recovery ratio and progression-free survival (PFS) prognosis. Magnetic Resonance Imaging (MRI) plays a crucial role in diagnosing GBM by utilizing various imaging modalities to provide valuable insights for personalized therapy. One significant goal of therapy is to delay tumor progression, measured using metrics such as PFS and overall response rate (ORR). Historical data have shown inconsistent results in tumor shrinkage, particularly in gliomas, underscoring the need for robust predictive models.

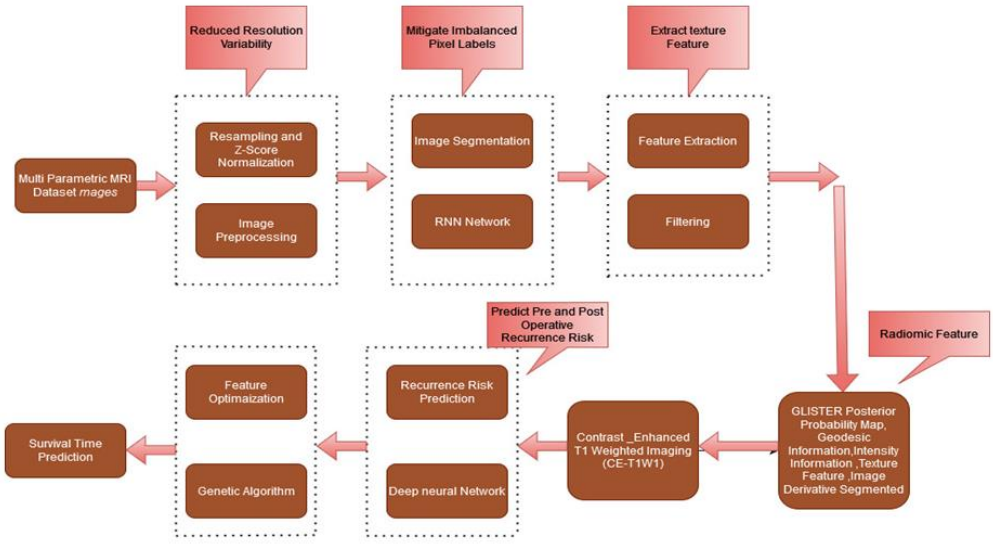

Figure 1 Proposed approach flow

The proposed methodology, outlined in Figure 1, involves several key steps: image preprocessing, Z-score normalization, resampling, tumor segmentation using generalized adversarial networks, texture feature extraction with wavelet-based band-pass filters, and integrating results into a regression model for predicting recurrent glioblastoma. This study evaluates the pre- and postoperative recurrence risk among glioblastoma patients treated with a combination of bevacizumab and nivolumab. The training cohort comprised 84 patients, and the testing cohort included 42 patients, based on pretherapy imaging data. Tumor volumes were delineated from contrast-enhanced T1-weighted images, and radiomic feature-based MRI signatures were derived from multiparametric MRI data to assess their relationship with overall survival (OS) and PFS.

Using multi-scale textural features, the recurrence rate for GBM patients is predicted through the random forest (RF) method. Texture features from MRIs were extracted using contrast-enhanced T1-weighted MRI (CE-T1W-MRI) data. The detailed steps are described in the following sections.

3.1. Patient Population

This retrospective investigation was approved by the regional Institutional Review Board, and explicit informed consent was not required. A total of 126 patients with newly diagnosed gliomas, excluding Grade I, were included. Multiparametric MRI exams were performed before any treatment or surgery. A deep neural network (CNN VGG-16 Model) was used to create a prediction model, validated using a 10-fold cross-validation method. The effectiveness of the DL technique was assessed using bevacizumab and nivolumab, and clinical characteristics of the 126 individuals were recorded.

3.2. Multi-Parametric MRI Dataset

Multiparametric MRI-based radiomic analysis aids in precision medicine by providing guidance on imaging prognosis, diagnosis, and decision-making. The MP-MRI acquisition protocol includes diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and contrast-enhanced MRI (cMRI) for all patients.

3.3. Image Pre-Processing

Preprocessing steps are essential to minimize motion artifacts and biases due to inhomogeneous magnetic fields and body movements. This includes skull stripping, bias field correction, intensity normalization, resolution fluctuation reduction, and image co-registration.

3.4. Resampling Image Pixel

Radiomic features depend on pixel size and slice thickness, necessitating interpolation or pixel size resampling. The Intraclass Correlation Coefficient (ICC) evaluates feature robustness, calculated as follows:

$$ICC = \frac{BMS - EMS}{BMS + (k-1).EMS + \frac{k}{n}(JMS - EMS)}$$

Where n is the "number of patients", BMS is the "mean square for features", k is the "number of repeated acquisitions", EMS is the "error mean square", and JMS is the "mean square error". Above equation assesses the accuracy and consistency of numerical measurements within groups.

3.5. Z-Score Normalization

Z-score normalization involves removing the mean intensity of the area or image of interest and dividing each voxel value by the standard deviation depicted in following equation:

$$Z = \frac{X - \mu}{\sigma}$$

Where X is the "voxel value", μ the "mean", and σ is the "standard deviation". This ensures consistent voxel relationships and spatial arrangement across images.

3.6. Radiomic Feature Extraction

The radiomics signature is developed by combining features from original and derived images. Wavelet transform-based features significantly impact the radiomics signature model, predicting survival time (PFS and OS) with higher accuracy and speed than human visual detection.

3.7. Recurrence Risk Prediction

Predicting the likelihood of glioblastoma recurrence is crucial as survival rates improve and mortality decreases. This study aims to predict the recurrence of brain cancer over a five-year period using DNN and RF methods. RF is effective for classification tasks, feature relevance determination, and data balancing.

3.8. *Inheritable Bi-objective Combinatorial Genetic Algorithm*

Algorithm 1: INHERITABLE BI-OBJECTIVE COMBINATORIAL GENETIC ALGORITHM

Input: Expression profiles
Output: Reduced key set

```
Begin
Step 1: Initialize the population
        Initialize population with binary genes G1 and G2
        For each gene G1 and G2 in the population:
            Generate initial population randomly where G1, G2 ∈ {0, 1}
```

```
Step 2: Define fitness function
        Define fitness function as prediction accuracy after 10-fold cross-validation
Step 3: Main loop
        While (Stop condition not met) do
Step 4: Selection
        Select individuals for mating using tournament selection
Step 5: Crossover
         For selected individuals:
              Select two parents
              Perform orthogonal cross-over to produce offspring
Step 6: Mutation
        Randomly select individuals to undergo mutation
Step 7: Evaluation
         Evaluate the fitness of all individuals
Step 8: Replacement
        Replace individuals with the lowest performance with new ones
Step 9: Gene transformation
           For each gene in the population:
                If (condition met) then
                   Transform one gene bit from 1 to 0
  End While
End
```

4. Results and output

Table 2 Accuracy, Sensitivity and Specificity comparison Table

Method	Accuracy	Sensitivity	Specificity	Time
CNN-Inception-V3	94	94	81.09	20.34
CNN-AlexNet	82	80	96	73.97
VGG16	95	95	96	45.1
Proposed RNN-GAN Model	**95.11**	**96**	**98**	**9.45**

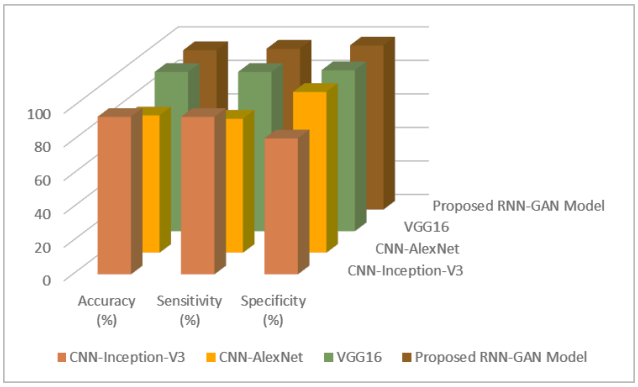

Figure 2 Accuracy, Sensitivity and Specificity comparison graph

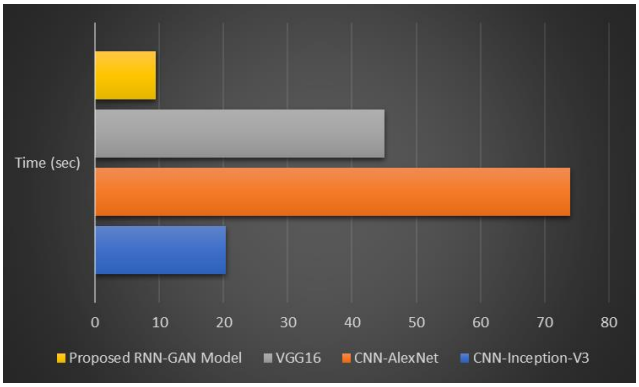

Figure 3 Time comparison graph

Table 3 Comparison of Model Architectures Based on Parameters and Layers

Method	Parameter	Layer
CNN-Inception-V3	24 million	43
CNN-AlexNet	60 million	13
VGG16	138 million	16
Proposed RNN-GAN Model	7 million	20

The performance of different models in predicting GBM recurrence was compared based on accuracy, sensitivity, specificity, and processing time as shown in table-2, figure-2,3. The models included CNN-Inception-V3, CNN-AlexNet, VGG16, and the proposed RNN-GAN model.

- **CNN-Inception-V3**: Achieved an accuracy of 94%, sensitivity of 94%, specificity of 81.09%, and processing time of 20.34 seconds.
- **CNN-AlexNet**: Demonstrated an accuracy of 82%, sensitivity of 80%, specificity of 96%, but had a longer processing time of 73.97 seconds.
- **VGG16**: Scored high with an accuracy of 95%, sensitivity of 95%, specificity of 96%, and a processing time of 45.1 seconds.
- **Proposed RNN-GAN Model**: Outperformed the other models with an accuracy of 95.11%, sensitivity of 96%, specificity of 98%, and the shortest processing time of 9.45 seconds.

The models were also evaluated based on the number of parameters and layers to understand their complexity and computational demands as depicted in table-3.

- **CNN-Inception-V3**: Contains 24 million parameters spread over 43 layers.
- **CNN-AlexNet**: Has 60 million parameters within 13 layers.
- **VGG16**: Includes a significant 138 million parameters across 16 layers.
- **Proposed RNN-GAN Model**: Is the most efficient, with only 7 million parameters distributed over 20 layers.

The proposed RNN-GAN model shows superior performance in predicting GBM recurrence compared to traditional models. It not only achieves the highest accuracy and specificity but also operates with the shortest processing time and fewer parameters, indicating its efficiency and potential for clinical application.

5. Conclusion and future scope

The comparative analysis of various machine learning models for predicting glioblastoma multiforme (GBM) recurrence highlights the effectiveness of the proposed RNN-GAN model. The RNN-GAN model demonstrated superior performance across multiple metrics, including accuracy (95.11%), sensitivity (96%), and specificity (98%), along with the shortest processing time of 9.45 seconds. This model's efficiency in handling data with fewer parameters (7 million) and an optimized number of layers (20) underscores its potential for clinical applications. The significant improvement over traditional models such as CNN-Inception-V3, CNN-AlexNet, and VGG16 suggests that integrating advanced deep learning architectures with robust radiomic features can substantially enhance the prediction of GBM recurrence. These findings emphasize the potential of the RNN-GAN model to aid clinicians in early detection and personalized treatment planning, ultimately improving patient outcomes and survival rates.

Future research can focus on integrating various types of multimodal data, including genomic, proteomic, and clinical data, alongside imaging data. This comprehensive approach can provide a more holistic view of the tumor's biological behavior and improve the predictive accuracy of recurrence. The integration of diverse data sources will enable the development of more sophisticated models that can capture the complex interactions within the tumor microenvironment, leading to more personalized and effective treatment strategies.

Another promising future direction is the real-time implementation and validation of the RNN-GAN model in clinical settings. This involves deploying the model in hospitals and medical centers to evaluate its performance in real-world scenarios. Real-time validation will help identify any practical challenges and allow for iterative improvements to the model. Additionally, conducting longitudinal studies to monitor patient outcomes over extended periods will provide valuable insights into the model's long-term efficacy and its potential impact on patient care.

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