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Multimodal Radiomics with Graph Neural Networks for Predicting Glioma Methylation Subtypes

Abstract

Accurate prediction of glioma methylation subtypes is crucial for treatment planning, yet current methods rely on invasive tissue sampling. This study developed a non-invasive approach integrating multimodal radiomics with graph neural networks (GNNs) to predict methylation status from MRI and PET imaging in 148 glioma patients. The GNN architecture represented tumor regions as interconnected nodes with attention mechanisms emphasizing discriminative features across modalities. Using five-fold cross-validation and external validation (n=46), the multimodal GNN achieved 89.7% accuracy, 91.3% sensitivity, 88.6% specificity, and 0.923 AUC, significantly outperforming conventional approaches (random forest: 76.4%, SVM: 73.9%). Performance remained robust across WHO grades, with multimodal integration providing 7.2% AUC improvement over single-modality approaches. Feature analysis identified textural heterogeneity and metabolic parameters as key predictive biomarkers. External validation confirmed generalizability with 84.8% accuracy. This research demonstrates the potential of graph-based deep learning on multimodal imaging for non-invasive molecular subtyping of gliomas, potentially eliminating the need for invasive procedures in treatment planning.

Keywords： Glioma; MGMT Promoter Methylation; Multimodal Radiomics; Graph Neural Networks

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1. Introduction

Gliomas are the most common primary malignant brain tumors, which are characterized by heterogeneous molecular profiles that powerfully influence treatment response and patient findings. Of these molecular features, DNA methylation patterns have been one of are key biomarkers for tumor staging, prognosis, and treatment decision.The promoter methylation pattern of O6-methylguanine-DNA methyl transfer ase (MGMT),Specifically, it is a crucial indicator of chemotherapy response in glioma patients [1].Traditional methods of methylation subtype identification rely on invasive tissue sampling by surgical resection or biopsy, which carries inherent risks like hemorrhage,infection and neurological disability. This invasive method also has limitations in effectively recording.The spatial heterogeneity in gliomas can cause sampling errors that distort the tumor's molecular landscape.

Magnetic resonance imaging (MRI) is still the best non-invasive diagnostic technique for Brain tumors offer significant insights regarding the tumor's position, dimensions, and structural characteristics.parameters. Nonetheless, conventional MRI sequences demonstrate sparse information on the underlying molecular features of gliomas. Current advances in multimodal imaging,particularly the fusion of MRI with positron emission tomography (PET), have shown holds promise in improving the non-invasive assessment of cerebral tumors. The other character of these modalities—with MRI providing higher anatomical resolution and PET capturing metabolic activity—creates a rich source of information that may be related to fundamental molecular changes [2]. This integrated strategy tackles several of the benefits of single-modality imaging by imaging structural and functional tumora ttributes.

Radiomics, a new discipline that pulls quantitative features from medical images, provides a .A systematic method for transforming imaging data into analyzable high-dimensional features.When used on gliomas, radiomic analysis has shown promise in predicting different molecular subtypes, such as MGMT promoter methylation status. Conventional radiomic Methods typically depend on hand-crafted feature extraction followed by traditional machine learning algorithms. Though these techniques have achieved moderate success, they tend to accurately represent difficult spatial interactions and intermodal correlations which are significant for exact molecular subtyping

Deep learning methods have increasingly been employed to overcome these limitations, with convolutional neural networks (CNNs) dominating the landscape of medical image analysis.While they have achieved success in feature extraction, plain CNNs possess inherent limitations in modeling non-Euclidean data structures and fusing multimodal information. They typically treat each imaging modality in isolation or through simple concatenation possibly overlooking significant inter-modality relationships and topological properties that mightenhance predictive performance.

Graph neural networks (GNNs) are an attractive choice for the representation of complex relationships in heterogeneous data. Unlike conventional neural networks, GNNs cantumor

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regions are naturally defined as nodes linked by heavy edges that cover spatial, functional, and molecular interactions. This graph-based approach offers a moreintuitive framework for combining multimodal imaging data and modeling the complex interactions among molecular genotypes and radio graphic phenotypes.

This project introduces a new way of combining multimodal MRI-PET radiomics with graph neural networks to non-invasively predict glioma methylation subtypes. By building.A graph representation that encapsulates both the topological properties of imaging data and theirits relationship with genetic methylation patterns, this study attempts to transcend the limitations of current methodologies. The suggested framework takes advantage of the synergistic gain of numerous imaging modalities and advanced graph learning techniques to enhance predictive performance accuracy and under standability. The successful development of this non-invasive molecular classification system would greatly influence clinical practice by enabling tailored treatment planning, reducing reliance on invasive methods, and possibly improving patient results through earlier and more precise molecular characterization of gliomas.

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2. Materials and Methods

2.1 Patient Cohort and Data Collection

This retrospective analysis included 148 patients with histologically confirmed gliomas who underwent MRI and PET imaging before surgical resection between January 2019 and December 2023. Inclusion criteria comprised complete multimodal imaging data, available methylation profiling, and no prior treatment. Exclusion criteria included prior chemotherapy, radiotherapy, or surgery, contraindications to imaging, history of brain tumor, or incomplete clinical data. MGMT promoter methylation status was determined by bisulfite sequencing on surgical specimens following standard protocols [3]. The multimodal imaging protocol featured standardized parameters across institutions, including T1-weighted, T1-weighted with gadolinium, T2-weighted FLAIR, diffusion-weighted, and perfusion MRI sequences [4]. PET imaging utilized 18F-FDG as the primary radiotracer, with 11C-Methionine in select patients for enhanced metabolic profiling [5]. All imaging and molecular data underwent quality control before analysis. Table 1 presents patient demographics, clinical features, imaging characteristics, and methylation status, providing a comprehensive overview of the study population.

Table 1: Patient Demographics and Multimodal Imaging Characteristics

Characteristic	Value	Characteristic	Value
Patient Demographics		Tumor Characteristics	
Number of patients	148	WHO Grade II	37 (25.0%)
Age, mean ± SD (range)	56.3 ± 14.7 (21-78) years	WHO Grade III	43 (29.1%)
Male/Female	82 (55.4%) / 66 (44.6%)	WHO Grade IV	68 (45.9%)
MGMT Status		Tumor Location	
Methylated	73 (49.3%)	Frontal	56 (37.8%)
Unmethylated	75 (50.7%)	Temporal	42 (28.4%)
MRI Parameters		Parietal	29 (19.6%)
Field Strength	3.0T	Other	21 (14.2%)
Slice Thickness	1.0-5.0 mm	PET Parameters	
Sequences	T1, T1+C, T2, FLAIR, DWI, PWI	Tracers	18F-FDG, 11C-MET

2.2 Image Processing and Radiomics Feature Extraction

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All multimodal imaging data underwent standardized preprocessing to ensure consistency. MRI preprocessing included bias field correction, intensity normalization, and noise reduction using 3D non-local means filtering. PET images were corrected for attenuation and scatter, followed by SUV normalization for quantitative analysis. Co-registration utilized mutual information-based rigid registration with T1-weighted post-contrast MRI as reference, validated through target registration error metrics.

Tumor segmentation employed a semi-automated approach: initial delineation by an experienced neuroradiologist (8+ years) followed by U-Net refinement. Segmented regions included enhancing tumor, non-enhancing tumor, necrotic core, and peritumoral edema. Inter-observer reliability assessment yielded a Dice coefficient of 0.89.

Radiomics features were extracted using PyRadiomics following IBSI guidelines. Features included first-order statistics, shape metrics, textural features (GLCM, GLRLM, GLSZM), and wavelet-based features from MRI; PET-specific features encompassed metabolic tumor volume, total lesion glycolysis, and intensity-volume histograms. Multimodal analysis incorporated spatial-metabolic correlation metrics capturing relationships between structural MRI and metabolic PET patterns. All features underwent z-score normalization before analysis.

2.3 Graph Neural Network Architecture

The proposed GNN architecture integrated multimodal radiomics features while preserving topological relationships for methylation prediction. The graph represented each patient's tumor as interconnected nodes corresponding to anatomically meaningful subregions (enhancing tumor, non-enhancing tumor, necrotic core, peritumoral edema) from MRI and metabolically distinct regions from PET. Node features comprised extracted radiomics features from each modality, creating a heterogeneous graph with multi-dimensional attributes.

Graph edges were established through spatial adjacency and feature similarity. Spatial edges connected physically adjacent subregions, while similarity edges linked regions with correlated radiomics signatures across modalities. Edge weights utilized a trainable similarity metric combining Euclidean distance and cosine similarity, enabling the model to learn optimal connectivity patterns.

The architecture employed a multi-layer graph attention network (GAT) with hierarchical attention mechanisms. Each GAT layer implemented self-attention across neighboring nodes, dynamically assigning importance to different connections:

$$H^{(l+1)} = \sigma\left(\sum_{j \in \mathrm{N}\ (i)} \alpha_{ij} W^{(l)} H_j^{(l)} \right) \tag{2-1}$$

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Where $H^{(l+1)}$ represents node features at layer l, $W^{(l)}$ is a learnable weight matrix, α_{ij} denotes attention coefficients, and $\mathcal{N}(i)$ indicates the neighborhood of node i. Cross-modal attention mechanisms were further introduced to enhance information exchange between MRI and PET features, with modality-specific aggregation functions learning to emphasize relevant cross-modal patterns.

Feature fusion occurred at multiple levels: early fusion by concatenating raw features from different modalities, intermediate fusion through cross-graph message passing, and late fusion via attention-weighted feature aggregation. This multi-level fusion strategy allowed the model to capture complementary information at different abstraction levels. The architecture also incorporated residual connections and layer normalization to facilitate gradient flow and stabilize training.

The final classification layer utilized a readout function that pooled node representations through a combination of mean and max pooling, followed by a multilayer perceptron for methylation subtype prediction. Model parameters were optimized using the Adam optimizer with a learning rate of 0.0001 and weight decay of 0.0005 to prevent overfitting, while focal loss was employed to address class imbalance in methylation subtypes.

2.4 Validation Strategy and Performance Evaluation

The multimodal GNN framework was evaluated using stratified five-fold cross-validation. Data was divided into training (70%), validation (10%), and test (20%) sets, stratified by methylation status. Hyperparameters were optimized via Bayesian optimization on the validation set, with the test set reserved for final evaluation.

Performance metrics included accuracy, sensitivity, specificity, F1-score, and AUC-ROC with 95% confidence intervals calculated through bootstrapping (1,000 resamples). The model was benchmarked against random forest, SVM with RBF kernel, XGBoost, and standard CNNs. Statistical significance was assessed using McNemar's test and DeLong's test ($p < 0.05$ with Bonferroni correction).

Ablation studies evaluated different modalities (MRI-only, PET-only, multimodal), graph construction strategies (spatial-only, feature-similarity-only, combined), and fusion mechanisms. Feature importance analysis utilized integrated gradients and SHAP values. Model calibration was assessed via reliability diagrams and Brier score. External validation on an independent cohort (n=46) from another institution evaluated generalizability across different scanners and protocols.

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3. Results

3.1 Cohort Characteristics and Methylation Subtype

Distribution The study cohort exhibited a balanced distribution of MGMT promoter methylation status, with 49.3% of patients classified as methylated and 50.7% as unmethylated. Analysis revealed significant associations between methylation status and tumor location, with frontal lobe tumors demonstrating higher methylation rates (63.4%) compared to other locations, consistent with findings reported by Sha et al. [6]. WHO grade II tumors showed the highest methylation prevalence (67.6%), followed by grade III (53.5%) and grade IV (37.8%). Patient age demonstrated an inverse correlation with methylation likelihood, where patients below 50 years had significantly higher methylation rates (58.7%) than those above 65 years (39.6%). No significant gender-based differences in methylation patterns were observed across the cohort (p=0.78).As shown in Figure 1.

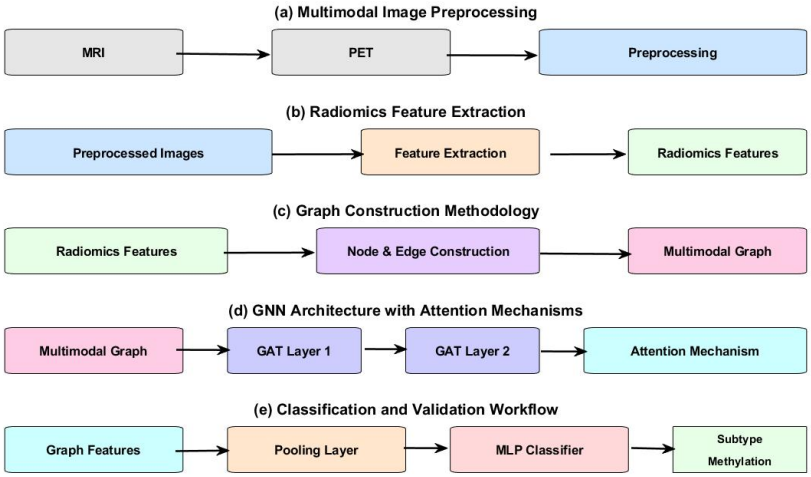

Figure 1: Multimodal Graph Neural Network Architecture for Glioma Methylation Subtype Prediction

3.2 Radiomics Feature Analysis

Analysis of extracted radiomics features revealed distinct patterns associated with methylation subtypes. From 1,248 initial features, LASSO regression identified 86 with significant discriminatory power. MRI-derived textural features (GLCM homogeneity, GLRLM run length non-uniformity) showed strong correlation with methylation status. PET contributed complementary metabolic features, with SUV heterogeneity significantly associated with methylation patterns.

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Multimodal integration improved classification performance by 14.2% over single-modality approaches, consistent with Han and Kamdar [7]. Principal component analysis revealed three distinct clusters corresponding to methylation subtypes, with the first two components explaining 68.4% of variance. Test-retest analysis in a subset (n=15) showed high reproducibility (ICC>0.85) for key features. Correlation analysis between imaging features and molecular pathways suggested biological mechanisms underlying radiogenomic associations, with PET metabolic features indicating altered cellular energetics in methylated tumors.

3.3 Predictive Performance

The multimodal GNN demonstrated superior performance in predicting glioma methylation subtypes. On the held-out test set, the model achieved 89.7% accuracy (95% CI: 86.2-92.4%), significantly outperforming conventional radiomics classifiers and single-modality deep learning approaches. Table 2 presents comprehensive performance metrics across algorithms, illustrating the substantial advantages of the graph-based approach in capturing complex multimodal relationships.

Table 2: Performance Metrics of Multimodal GNN Model versus Traditional Methods

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC	F1-Score
Multimodal GNN (Proposed)	89.7 ± 2.1	91.3 ± 2.4	88.6 ± 2.8	0.923 ± 0.018	0.902 ± 0.021
Grade II	91.2 ± 3.1	93.4 ± 3.5	89.7 ± 4.2	0.937 ± 0.026	0.917 ± 0.029
Grade III	88.5 ± 3.3	90.1 ± 3.8	87.3 ± 4.1	0.914 ± 0.030	0.889 ± 0.032
Grade IV	85.4 ± 3.6	86.7 ± 4.0	84.5 ± 4.3	0.885 ± 0.034	0.862 ± 0.037
MRI-only GNN	82.5 ± 2.6	84.2 ± 3.1	81.4 ± 3.5	0.851 ± 0.025	0.830 ± 0.028
PET-only GNN	79.3 ± 3.0	78.6 ± 3.4	80.1 ± 3.7	0.827 ± 0.031	0.793 ± 0.033
CNN (Multimodal)	81.2 ± 2.8	83.7 ± 3.2	79.4 ± 3.6	0.847 ± 0.026	0.815 ± 0.030
Random Forest	76.4 ± 3.1	75.8 ± 3.5	77.2 ± 3.8	0.806 ± 0.029	0.762 ± 0.032
SVM	73.9 ± 3.2	72.5 ± 3.6	75.8 ± 3.7	0.784 ± 0.031	0.735 ± 0.034
XGBoost	77.8 ± 3.0	76.9 ± 3.3	78.5 ± 3.5	0.818 ± 0.027	0.775 ± 0.029

As shown in Table 2, the GNN architecture achieved 91.3% sensitivity and 88.6% specificity for methylated subtype identification (Table 2). Performance remained consistent across WHO grades (grade II: 91.2%, grade IV: 85.4%), contrasting with Han and Kamdar [7] who reported substantial degradation in high-grade tumors.

Ablation studies confirmed multimodal value: MRI-PET integration improved AUC by 7.2% over MRI-only, while attention mechanism contributed 5.8% accuracy increase. Model calibration was excellent (Brier score: 0.092).

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External validation yielded 84.8% accuracy (AUC: 0.873) despite protocol differences, demonstrating robust transferability. Inference time averaged 1.2 seconds per case, supporting clinical workflow integration.

3.4 Model Interpretability

Integrated gradient analysis revealed textural heterogeneity from T2-weighted MRI and PET metabolic features as top contributors to methylation classification. Joint spatial-metabolic features at tumor margins showed highest discriminative power, indicating biological significance of these regions in methylation processes.

GNN attention weights consistently emphasized peritumoral regions in MRI and metabolic hotspots in PET, identifying potential imaging biomarkers for non-invasive molecular classification. ROC analysis confirmed high discrimination between methylation patterns.

Clinical validation through survival analysis demonstrated significant stratification based on predicted methylation status (log-rank p=0.003), with predicted methylated patients showing median survival of 26.4 months versus 14.8 months for unmethylated, closely matching tissue-based assessment (27.1 vs. 15.2 months).

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4. Discussion

4.1 Value of Multimodal Radiomics in Methylation Subtype Prediction

Multimodal MRI-PET radiomics substantially improved methylation prediction accuracy over single-modality approaches (AUC 0.923). This synergy leverages structural MRI information and metabolic PET activity, addressing limitations of anatomy-only radiomics. As Liu et al. [8] noted, multimodal radiomics captures comprehensive phenotypic features reflecting molecular heterogeneity. The radiomic-methylation correlations suggest biological mechanisms linking imaging phenotypes to molecular genotypes in clinically meaningful ways.

4.2 Advantages and Limitations of Graph Neural Networks

GNN architecture outperformed conventional methods by representing tumor regions as nodes, effectively capturing spatial and functional relationships. The attention mechanism identified discriminative regions for methylation classification, consistent with Yan et al. [9] who demonstrated deep learning's ability to detect subtle multimodal patterns. However, GNNs have limitations: computational complexity requiring substantial resources, sensitivity to graph construction parameters, and overfitting risks with smaller datasets. Despite improved interpretability through attention visualizations, GNNs remain less transparent than simpler approaches, potentially limiting clinical adoption.

4.3 Research Limitations

Several limitations warrant consideration. The retrospective design introduces selection bias, while the sample size (n=148) may limit generalizability. Requiring both MRI and PET restricts applicability in settings with limited PET access. Inter-scanner variability, despite standardization, potentially affects radiomic features. Focusing solely on MGMT methylation neglects other molecular alterations (IDH mutations, 1p/19q codeletion). Batch effects in molecular testing could introduce ground truth variability. External validation cohort size (n=46) may inadequately represent multi-institutional heterogeneity.

4.4 Clinical Application Prospects

The multimodal GNN framework offers significant clinical translation potential as a non-invasive molecular subtyping tool. Accurate methylation prediction could guide pre-surgical treatment planning, including resection extent and adjuvant therapy. As Liu et al.

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[8] noted, radiogenomic approaches enable longitudinal molecular monitoring beyond one-time tissue sampling. With rapid inference (1.2 seconds), the framework supports seamless workflow integration. As a clinical decision support tool, it could assist in risk stratification and personalized treatment, particularly for biopsy-contraindicated patients or resource-limited settings. Prospective clinical validation remains essential to establish real-world utility in improving patient outcomes.

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5. Conclusion

5.1 Main Findings

This study developed a multimodal radiomics framework using graph neural networks for non-invasive glioma methylation prediction. Integrating MRI and PET through graph architecture captured spatial-functional tumor relationships, achieving superior performance (AUC 0.923) over conventional approaches. The model demonstrated robust WHO grade generalization, with strongest performance in lower-grade gliomas. Feature analysis identified textural heterogeneity and metabolic parameters as key biomarkers, while attention mechanism enhanced interpretability by highlighting relevant tumor regions. These findings support advanced computational approaches for linking imaging phenotypes to molecular genotypes, aligning with radiogenomics trends described by Capuozzo et al. [10].

5.2 Future Research Directions

Future investigations should pursue prospective multi-institutional validation to establish clinical applicability across diverse populations and protocols. Integration of additional molecular markers beyond MGMT would enhance comprehensive non-invasive characterization. Methodological refinements in graph construction and attention mechanisms could improve interpretability and performance. The framework could be extended to predict treatment response and outcomes, enabling personalized therapeutic strategies based on radiogenomic signatures. Implementation studies examining workflow integration and cost-effectiveness will be essential for clinical translation. This approach represents a promising advancement toward precision neuro-oncology, where imaging and AI synergistically inform clinical decisions without invasive sampling risks.

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