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Innovative imaging techniques for early glioma detection and characterization: a systematic review and meta-analysis

Técnicas de imagem inovadoras para detecção e caracterização precoce de glioma: uma revisão sistemática e meta-análise

Técnicas innovadoras de diagnóstico por imágenes para la detección y caracterización temprana del glioma: una revisión sistemática y metanálisis

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The findings emphasize the critical role of integrated imaging approaches, such as the combination of DTI, PET, and advanced MRI techniques, in improving the diagnostic accuracy of gliomas. These innovations enhance the ability to differentiate tumor grades, detect malignant transformations, and evaluate tumor biology, which is crucial for tailoring treatment strategies and improving patient outcomes.
Originality/value:
This systematic review and meta-analysis contribute significant value by providing a comprehensive evaluation of recent imaging innovations, underscoring the enhanced diagnostic precision achieved through the integration of various advanced techniques. The study's originality lies in its synthesis of recent data, offering robust evidence on the effectiveness of combining imaging modalities for more accurate glioma characterization.

ABSTRACT

Background: Gliomas, primary intra-axial brain tumors originating from neuroglial cells, pose diagnostic challenges despite advancements in imaging techniques. This systematic review and meta-analysis aimed to evaluate recent innovations in imaging modalities for glioma detection and characterization. **Methodology**: A comprehensive search of PubMed and Cochrane Library identified studies from 2015 to December 2023. Inclusion criteria encompassed studies on imaging techniques for gliomas, published in peer-reviewed journals. Quality was assessed using the Newcastle-Ottawa Scale. **Results**: Fifteen studies on glioma grades and imaging techniques were reviewed. Diffusion Tensor Imaging (DTI) was practical for glioma characterization, with Apparent Diffusion (AD) maps accurately detecting malignant transformation and differentiating tumor grades. 18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG PET) enhanced glioma identification, particularly when combined with MRI, improving specificity for high-grade tumors. Advanced MRI techniques, such as MR Perfusion Imaging, and Dynamic 18F-FET PET were useful for distinguishing glioma grades and evaluating tumor biology. Amide Proton Transfer Imaging, in conjunction with FDG-PET, also enhanced diagnostic precision. The meta-analysis showed a combined effect size of 0.8622 (95% CI [0.6401; 1.0843]) for ADC in gliomas, indicating a high diagnostic value. **Conclusion**: Recent advancements in DTI and PET significantly improve glioma detection and characterization, highlighting the need for integrated imaging for accuracy..

Keywords: Gliomas, Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), Apparent Diffusion Coefficient (ADC), Magnetic Resonance Imaging (MRI), Tumor Characterization.

RESUMO

Introdução: Os gliomas, tumores cerebrais intra-axiais primários que se originam nas células neurogliais, representam desafios diagnósticos, apesar dos avanços nas técnicas de imagem. Esta revisão sistemática e meta-análise tem como objetivo avaliar as inovações recentes nas modalidades de imagem para a detecção e caracterização do glioma. **Metodologia**: Foi realizada uma busca abrangente no PubMed e na Biblioteca Cochrane por estudos identificados de 2015 a dezembro de 2023. Os critérios de inclusão incluíram estudos sobre técnicas de imagem para gliomas, publicados em periódicos revisados por pares. A qualidade foi avaliada por meio da escala de Newcastle-Ottawa. **Resultados**: Quinze estudos sobre graus de glioma e técnicas de imagem foram revisados. A imagem por tensor de difusão (DTI) foi eficaz para a caracterização do glioma, com mapas de difusão aparente (DA) detectando com precisão a transformação maligna e diferenciando os graus do tumor. A tomografia por emissão de pósitrons com 18F-fluorodesoxiglicose (18F-FDG PET) melhorou a identificação do glioma, especialmente quando combinada com a ressonância magnética, o que melhorou a especificidade de tumores de alto grau. Técnicas avançadas de ressonância magnética, como imagem de perfusão e 18F-FET PET dinâmico, foram úteis para distinguir os graus de glioma e avaliar a biologia do tumor. A imagem de transferência de prótons de amida, juntamente com o FDG-PET, também melhorou a precisão do diagnóstico. A metanálise mostrou um tamanho de efeito combinado de 0,8622 (IC 95% [0,6401; 1,0843]) para ADC em gliomas, sugerindo um alto valor diagnóstico. **Conclusão**: Avanços recentes em DTI e PET melhoram significativamente a detecção e caracterização de gliomas, destacando a necessidade de imagens integradas para maior precisão.

Palavras-chave: Gliomas, Diffusion Tensor Imaging (DTI), Tomografia por Emissão de Pósitrons (PET), Coeficiente de Difusão Aparente (ADC), Ressonância Magnética (MRI), Caracterização de Tumores.

RESUMEN

Introducción: Los gliomas, tumores cerebrales intra axiales primarios que se originan en células neurogliales, plantean desafíos diagnósticos a pesar de los avances en las técnicas de imagen. Esta revisión sistemática y metaanálisis tienen como objetivo evaluar las innovaciones recientes en las modalidades de diagnóstico por imágenes para la detección y caracterización del glioma. **Metodología**: Se realizó una búsqueda exhaustiva en PubMed y en la Biblioteca Cochrane de estudios identificados desde 2015 hasta diciembre de 2023. Los criterios de inclusión abarcaron estudios sobre técnicas de imagen para gliomas, publicados en revistas revisadas por pares. La calidad se evaluó mediante la escala de Newcastle-Ottawa. **Resultados**: Se revisaron quince estudios sobre los grados de glioma y las técnicas de imagen. Las imágenes con tensor de difusión (DTI) fueron eficaces para la caracterización del glioma, con mapas de difusión aparente (AD) que detectaron con precisión la transformación maligna y diferenciaron los grados tumorales. La tomografía por emisión de positrones con 18F-fluorodesoxiglucosa (PET con 18F-FDG) mejoró la identificación del glioma, especialmente cuando se combinó con la resonancia magnética, lo que mejoró la especificidad de los tumores de alto grado. Las técnicas avanzadas de resonancia magnética, como la resonancia magnética por imágenes de perfusión y la TEP dinámica con 18F-FET, fueron útiles para distinguir los grados de glioma y evaluar la biología tumoral. Las imágenes de transferencia de protones de amida, junto con FDG-PET, también mejoraron la precisión diagnóstica. En el metanálisis se observó un tamaño del efecto combinado de 0,8622 (IC 95 % [0,6401; 1,0843]) para el ADC en los gliomas, lo que indica un valor diagnóstico alto. **Conclusión**: Los avances recientes en DTI y PET mejoran significativamente la detección y caracterización del glioma, lo que pone de manifiesto la necesidad de obtener imágenes integradas para mayor precisión.

Palabras clave: Gliomas, imágenes con tensor de difusión (DTI), tomografía por emisión de positrones (PET), coeficiente de difusión aparente (ADC), resonancia magnética (RM), caracterización tumoral.

INTRODUCTION

Primary intra-axial brain tumors that are most often seen are gliomas. Neuroglial cells, the supporting tissue of the central nervous system (CNS), are the source of gliomas. It is made up of oligodendrocytes and astrocytic components that are differentiated. Gliomas are classified as low-grade (LGGs, grade I–II) or high-grade (HGGs, grade III–IV) in the 2016 World Health Organization (WHO) classification of CNS malignancies (Gupta & Dwivedi, 2017). Every year, gliomas are diagnosed in around 100,000 individuals globally. Gliomas are linked to significant rates of death and morbidity even though they make up less than 2% of all newly diagnosed malignancies. Approximately 70–75% of all gliomas are grade IV gliomas, previously known as glioblastoma multiforme (GBM), which is the deadliest kind of glioma with a median overall survival (OS) of 14–17 months (Ferlay et al., 2019; Quartuccio & Asselin, 2017).

A brain abscess or other inflammatory and infectious disorders are the primary differential diagnosis for gliomas, along with other brain cancers such intracranial lymphoma and metastases (Chiavazza et al., 2018). To distinguish gliomas from other brain diseases and separate LGGs from HGGs in this case, the pre-surgical diagnostic work-up need to be predicated on a multimodal imaging technique (Mellai et al., 2015). Frequently, gliomas return in the vicinity of the surgical cavity (Ferlay et al., 2019). It is challenging for imaging modalities to identify recurrence against the backdrop of parenchymal abnormalities associated with prior therapies, such as radiation (RT) and surgery. RT combined with the alkylating drug temozolomide is the mainstay of therapy, especially after surgery. Additionally, medications like bevacizumab that target the vascular endothelial growth factor (VEGF) have been developed to treat recurrent GBM (Ellingson et al., 2017). Radiation necrosis (RN), pseudo-progression, and pseudo-response are examples of post-treatment changes that may occur after these therapies (Zikou et al., 2018). Consequently, when it comes to clinical care, multimodal imaging may be crucial (Quartuccio, et al., 2020).

When a patient has glioma, which manifests as a hypodense lesion and may exhibit rim enhancement, a brain computed tomography (CT) scan is often the first imaging modality used (Abd-Elghany et al., 2019). Though CT offers valuable anatomical information, it is often followed by magnetic resonance imaging (MRI) (Quartuccio, et al., 2020), which is better than CT in most cases of brain malignancies and may give additional information (Park et al., 2014; Quartuccio et al., 2020). It is usual procedure to use diffusion weighted imaging (DWI), T2-weighted (T2-w), T2-fluid-attenuated inversion recovery (T2-FLAIR), T1-weighted (T1-w), and T1-w contrast-enhanced (T1-CE) sequences while conducting an MRI (Shukla et al., 2017; Thust et al., 2018). When evaluating brain tumors and giving details on their location, mass effect, peritumoral edema, and contrast-enhancing, magnetic resonance imaging (MRI) with gadolinium (Gd) contrast enhancement is regarded as the gold standard imaging technique. Gliomas, however, are not always able to be confidently distinguished from other brain cancers, such as primary central nervous system lymphoma (PCNSL) and metastases, or from non-neoplastic lesions, such as brain abscesses or parasite lesions (Chiavazza et al., 2018). With the gradual introduction of diffusion, perfusion-weighted, and spectroscopic sequences in the clinical context, sophisticated "functional" MRI approaches have recently surfaced for the evaluation of brain malignancies (Quartuccio et al., 2020).

Glioblastoma diagnosis, prognosis, and monitoring have all benefited greatly by the use of Positron Emission Tomography (PET). It provides greater insights into the biology characteristics of these brain tumors than magnetic resonance imaging (MRI) does. The extra data is very helpful for non-invasive grading, differential diagnosis, defining the size of the tumor, surgical planning, radiation, and post-treatment monitoring. Radiotracers associated with glucose metabolism and those associated with amino acid transport are the two main kinds of radiotracers that are most often utilized in clinical applications to image glioblastomas (Drake et al., 2020). Regarding glioma grading and prognosis, both kinds of tracers provide important information. O-(2-18F-fluoroethyl)-L-tyrosine (FET) (18F-FET), carbon-11-methyl-L-methionine (MET) (11C-MET), 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (FDOPA) (18F-FDOPA), α-[11C] methyl-l-tryptophan (AMT) (11C-AMT), and 18F-fluciclovine (18F-FACBC) are amino acid tracers that have a lower uptake in normal brain tissue and are excellent in helping to define the extent of the tumor, develop treatment plans, and enable follow-up. Their primary characteristic is that they show a decreased uptake in normal brain tissue, which creates a stark difference between the two types of brain tissue. This capacity is superior to that of 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) in the imaging of brain tumors (Verger & Langen, 2017). Radiation-labeled amino acid PET imaging has made revolutionary strides recently. Due to these initiatives, the worldwide Response Assessment in Neuro-Oncology (RANO) working group has recommended amino acid PET as a crucial supplementary technique for brain tumor diagnosis (Law et al., 2019). The expanding significance of PET in improving our knowledge and treatment of glioblastomas is shown by this acknowledgment.

The usefulness of imaging methods for glioma diagnosis and treatment has been emphasized in several reviews of the literature. Yang and colleagues assessed the efficacy of combining MRI and PET-CT, utilizing distinct tracers (Yang et al., 2019). They determined that this method improves diagnostic precision, but they also identified notable drawbacks, including small sample sizes, limited representativeness, and inconsistent outcomes because different PET tracers provide different information. Likewise, Shaffer et al, examined the application of ultra-high-field (UHF) 7T MRI, highlighting its enhanced

resolution and capacity to discern microstructures and forecast tumor classification; however, the review was confined to UHF MRI and did not encompass all accessible imaging modalities or contemporary developments (Shaffer et al., 2022). These reviews underscore the potential of advanced imaging techniques for glioma diagnosis but reveal a literature gap, as they do not provide comprehensive evidence on all imaging modalities or include the most recent developments in these technologies. This gap underscores the need for our systematic review, which aims to provide an up-to-date and inclusive evaluation of the latest advancements in imaging techniques for the early detection and characterization of gliomas. This systematic review and meta-analysis aim to critically evaluate the advancements in imaging techniques for the early detection and characterization of gliomas. It will focus on studies that have assessed the utility of advanced imaging modalities, including but not limited to diffusion tensor imaging (DTI), functional MRI, and various PET imaging techniques, in the diagnosis, grading, and molecular characterization of gliomas.

METHODOLOGY

Study Design

This systematic review and meta-analysis focused on evaluating advancements in imaging techniques for the early detection and characterization of gliomas. The review synthesized data from studies assessing the diagnostic accuracy and clinical utility of various imaging modalities, including Diffusion Tensor Imaging (DTI), 18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG PET), and advanced MRI techniques.

Sample Selection

The search strategy aimed to systematically identify relevant studies on imaging techniques used for glioma detection and characterization. A comprehensive search was conducted using databases such as PubMed and Cochrane Library. Keywords and MeSH terms included "glioma," "imaging techniques," "Diffusion Tensor Imaging," "DTI," "18F-FDG PET," "MRI," and "glioma characterization." Boolean operators (AND, OR) were utilized to refine the search results.

Inclusion Criteria

- Studies investigating imaging techniques for early detection and characterization of gliomas.
- Research articles written in English.
- Studies involving human subjects with gliomas.
- Articles published between 2015 and December 2023.
- Publications in peer-reviewed journals.
- Studies providing quantitative data on imaging techniques and their diagnostic performance.

Exclusion Criteria

- Review articles, editorials, letters, and conference abstracts.
- Studies focusing on imaging techniques without evaluating their clinical utility in glioma detection or characterization.
- Studies not specifically addressing glioma detection or characterization.
- Non-English articles.
- Studies with insufficient or unclear methodology and data.

Study Method

Electronic databases were searched for relevant articles, and studies were screened based on titles and abstracts. Full texts of selected articles were then reviewed to determine eligibility based on the inclusion and exclusion criteria. Studies meeting the criteria were included in the review and meta-analysis.

Sample Size

A total of 15 studies were included in the systematic review, with 3 studies included in the meta-analysis.

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. Two independent reviewers conducted the quality assessment, and any discrepancies were resolved through discussion or consultation with a third reviewer.

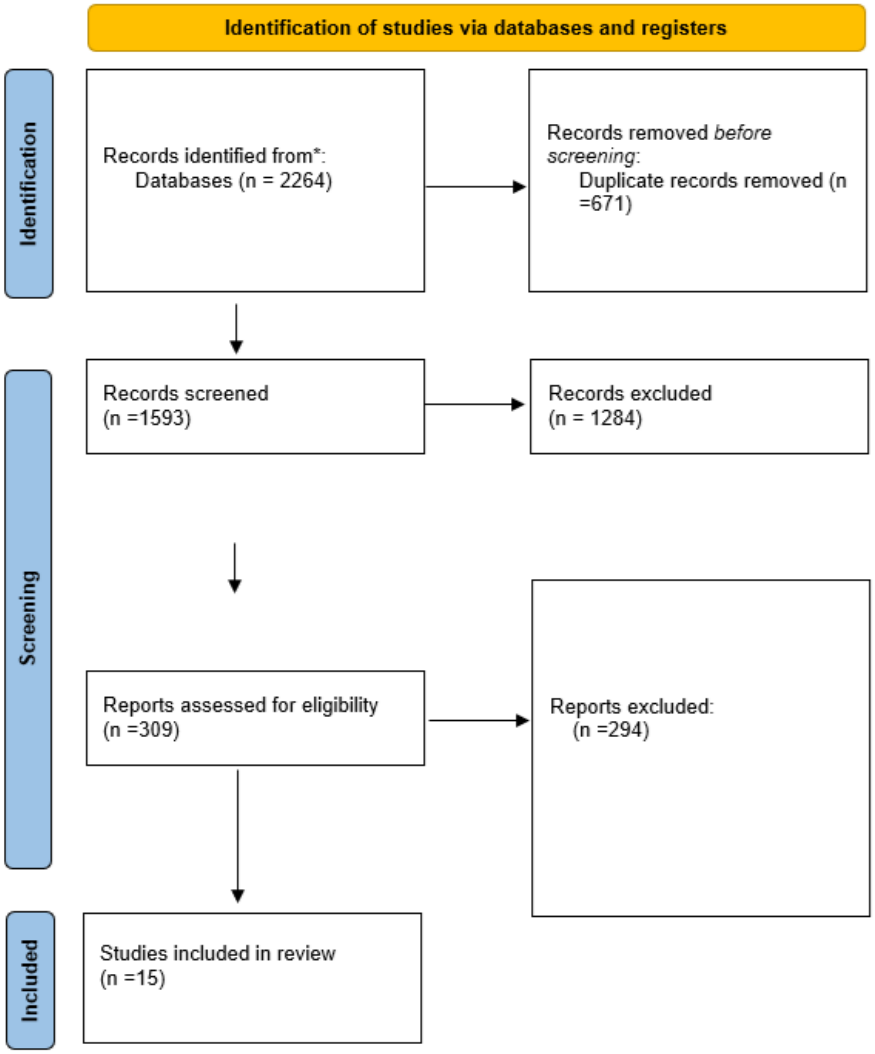
Data Extraction

Data were extracted from the selected studies using a standardized form. Information such as study characteristics (e.g., author, publication year), imaging techniques used, patient populations, and diagnostic outcomes were systematically recorded with results statistics.

Data Analysis

A meta-analysis was conducted to synthesize quantitative data across studies. Effect sizes, such as fixed and random effects models were calculated as applicable. Statistical heterogeneity was assessed using the I^2 statistic, with values indicating the degree of variability between studies. Random-effect models were used to account for variability, and sensitivity analyses were performed to test the robustness of the findings. Subgroup analyses were also conducted to explore the impact of different imaging modalities on glioma detection and characterization.

Table 1. PRISMA Diagram with the literature review flow



Source: Authors' development.

RESULTS AND DISCUSSION

2264 publications in all were found during the first literature search. Following a meticulous assessment of abstracts and titles,309 articles were deemed relevant, and their full texts were acquired for further examination. Excluded studies did not fulfill the inclusion criteria or did not explicitly investigate advancements in imaging techniques in detecting gliomas. After a thorough screening procedure, 14 papers were found to be appropriate for the systematic review and meta-analysis.

Study characteristics:

Fifteen studies were included in the systematic review of advancements in imaging techniques for early detection and characterization of gliomas. Most studies (n = 12, 80%) were retrospective cohort studies; the remaining studies (n = 3, 20%) were comparative assessments. The studies addressed a variety of glioma forms, including low-grade and high-grade variations, with sample sizes ranging from 23 to 162 individuals.

Diffusion Tensor Imaging (DTI) (n = 5), 18F-FET PET (n = 4), FDG-PET/CT (n = 3), MR Perfusion Imaging (n = 1), IVIM-MR Imaging (n = 1), and 11C-Methionine PET (n = 1) were among the imaging modalities evaluated. Study-specific outcomes that were assessed included malignant transformation, tumor recurrence, glioma grading, response to treatment, and the ability to distinguish gliomas from other brain lesions. The research used a variety of metrics and parameters, such as the Tumor-to-Brain Ratio (TBR), Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), and values obtained from PET and MRI.

Together, the research sought to use modern imaging methods to increase knowledge of glioma behavior and improve diagnosis accuracy. With variable degrees of sensitivity, specificity, and overall diagnostic performance, the findings demonstrated the value of these approaches in monitoring treatment response, early diagnosis, and glioma grade differentiation (Table 1).

Diffusion Tensor Imaging (DTI):

Glioma characterization and early identification have found a useful use for Diffusion Tensor Imaging (DTI). In resected WHO II low-grade gliomas, Freitag et al. (2016) discovered that DTI, more especially employing Apparent Diffusion (AD) maps, showed the greatest diagnostic accuracy for identifying malignant transformation (MT). The area under the curve (AUC) for AD maps was 0.96 ($p<0.0001$), indicating a sensitivity of 94.94% and specificity of 89.7%. Furthermore, MT may be detected up to 0.8±0.5 years sooner with DTI compared with traditional T1-weighted contrast-enhanced imaging ($p=0.028$). Jin et al. (2016) emphasized the usefulness of DTI in glioblastoma recurrence surveillance, reporting substantial decreases in both Neurite Density Index (NDI) and Fractional Anisotropy (FA) up to two months before to clinical recurrence, with NDI decreasing by 6.4% and FA by 11.2% ($p<0.05$). In order to distinguish between low-grade and high-grade gliomas, Shan et al. (2017) used DTI. They discovered that FA and ADC values offered insightful information, with ADC showing superior specificity for high-grade tumors. In order to evaluate WHO grading and prognosis in non-enhancing gliomas, Takano et al. (2016) combined DTI with other imaging modalities, highlighting its function in tumor characterisation. Furthermore, Sakata et al. (2018) showed that Minimum ADC values were useful in differentiating between high-grade and low-grade gliomas, especially in conjunction with other imaging modalities.

18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG PET):

Glioma identification and characterisation have benefited greatly by 18F-FDG PET. FDG-PET/CT alone exhibited lower sensitivity (59%) and specificity (79%), but when paired with MRI, it obtained 100% specificity for diagnosing high-grade gliomas (Shaw et al., 2019). According to this, FDG-PET/CT is useful, but its effectiveness is increased when combined with MRI. In order to track the treatment response in WHO grade II gliomas, Roelcke et al. (2016) assessed Amino Acid PET, which is connected to FDG-PET. After 2.3 months on PET compared to 16.8 months on MRI, they discovered that PET was superior to MRI. A decrease in active tumor volume predicted progression-free survival (PFS) of 60 months ($P=0.018$) and 48 months ($P=0.037$). After 2.3 months on PET, there was a 25% reduction in active tumor volume. Using 18F-FET PET, Verger et al. (2017) were able to distinguish between IDH-mutated astrocytomas and IDH wild-type glioblastomas with a cut-off for Tumor-to-Brain Ratio (TBRmean) of 1.95 and a sensitivity of 89% and specificity of 67%. According to Song et al. (2016), 18F-FDG PET-CT demonstrated improved overall sensitivity, specificity, and accuracy in the diagnosis and grading of gliomas than MRI. FDG-PET has been shown to be useful in discriminating between glioblastoma and primary central nervous system lymphoma (PCNSL), as indicated by Nakajima et al. (2014). While FET PET by itself could not substitute histological confirmation, Bashir et al. (2018) pointed out that it was helpful in locating active tumor regions and evaluating the biology of low-grade gliomas.

MRI:

Significant progress has been made in the identification and characterisation of gliomas using MRI. In order to distinguish between gliomas, Aprile et al. (2015) analyzed MR Perfusion Imaging utilizing Cerebral Blood Volume (CBV) and Perfusion-Sensitive Ratio (PSR). They discovered that low-grade and high-grade gliomas differed significantly, with PSR demonstrating the best sensitivity and specificity, especially when it came to differentiating between low-grade and grade III gliomas. In order to improve glioma characterisation, Vomacka et al. (2018) used Dynamic 18F-FET PET in combination with voxel-wise MRI analysis. In comparison to conventional volume-of-interest (VOI) approaches, their research provided a more thorough evaluation by revealing substantial variations in metrics such as Tumor-to-Brain Ratio (TBR), Time-to-Peak (TTP), and Slope15–40 across WHO grades and IDH mutation status.

In order to assess glioblastoma, Valentini et al. (2017) merged advanced and conventional MRI with 18F-FDG PET/CT. They found that the most malignant tumor morphologies were correlated with the greatest SUVmax, rCBV, Cho/Cr, and Cho/NAA ratios in contrast-enhancing areas. This method worked well for identifying biological differences among glioblastomas. Yamashita et al. (2016) discovered that the combination of FDG-PET and IVIM-MR Imaging yielded useful quantitative data for distinguishing between Glioblastoma Multiforme (GBM) and Primary Central Nervous System Lymphoma (PCNSL), with metrics such as fmax and Dmin enhancing diagnostic performance. Sakata et al. (2018), in closing, emphasized the additional diagnostic use of Amide Proton Transfer Imaging in conjunction with FDG-PET/CT, improving the ability to distinguish between high-grade and low-grade gliomas.

Table 1. Characteristics and results of the studies reviewed

Author(s)	Year	Study Design	Population Type and Number	Imaging Technique	Outcomes Assessed	Results with Stats	Conclusion
Freitag, M.T. et al. (Freitag et al., 2016)	2016	Retrospective cohort study	47 patients with resected WHO II low-grade glioma	Diffusion Tensor Imaging (DTI)	Detection of malignant transformation (MT) using AD, MD, RD maps	ADmin had the best diagnostic value for MT detection (sensitivity/specificity: 94.94%/89.7%, AUC: 0.96, p<0.0001). Cohen's Kappa: ADmin (0.77), MDmin (0.71), RDmin (0.65), p<0.0001. Detection time gain using DTI: 0.8±0.5 years, p=0.028.	DTI can detect MT at the same time or earlier than T1-weighted contrast-enhanced images, with AD showing the highest sensitivity, specificity, and tumor contrast.
Jin, Y. et al. (Jin et al., 2020)	2020	Retrospective cohort study	30 patients with glioblastoma	Diffusion Tensor Imaging (DTI)	Detection of glioblastoma recurrence using FA and NDI	FA and NDI showed significant changes 2 months before recurrence (FA: 11.2% lower, NDI: 6.4% lower; p<0.05).	FA and NDI in DTI may serve as non-contrast biomarkers for detecting subclinical glioblastoma recurrence.
Shan, W. et al. (*Clinical Application Value of 3.0T MR Diffusion Tensor Imaging in Grade Diagnosis of Gliomas*, n.d.)	2017	Retrospective cohort study	31 patients with glioma (14 low-grade, 17 high-grade)	3.0T MR Diffusion Tensor Imaging (DTI)	Differentiation of glioma grade using FA and ADC values	Low-grade glioma: FA (139.4±81.3), ADC (1.36±0.21) x10^-3 mm²/sec. High-grade glioma: FA (103.1±41.5), ADC (1.09±0.28) x10^-3 mm²/sec. ADC AUC: 0.79, FA AUC: 0.62. Sensitivity/specificity for ADC: 58.8%/92.9%, FA: 94.1%/35.7%.	FA and ADC values in DTI are valuable for estimating the pathological grade of glioma, with ADC providing better specificity for high-grade tumors.
Shaw, T.B. et al.(Shaw et al., 2019)	2019	Retrospective cohort study	33 patients with suspected or known glioma	FDG-PET/CT and Gadolinium-enhanced MRI	Identification of high-grade glioma (WHO III/IV)	FDG-PET/CT: Sensitivity 59%, Specificity 79%, PPV 81%, NPV 55%. MRI: Sensitivity 77%, Specificity 86%, PPV 89%, NPV 71%. Combined: Specificity 100%, PPV 100%, Sensitivity 79%, NPV 75%.	Combining FDG-PET/CT with MRI improves identification of high-grade glioma compared to each modality alone, but a negative FDG-PET/CT should not rule out surgery.
Roelcke, U. et al. (Roelcke et al., 2016)	2016	Retrospective cohort study	33 patients with WHO grade II glioma	Amino Acid PET and MRI	Monitoring chemotherapy response, seizure control, progression-free survival (PFS)	PET response: 25% reduction in active volume after 2.3 months. MRI response: 25% reduction after 16.8 months. Decrease in active tumor volume predicts PFS ≥60 months (P=0.018) and ≥48 months (P=0.037).	Amino acid PET is superior to MRI in evaluating chemotherapy response in WHO grade II glioma, and may guide personalized treatment duration.
Verger, A. et al. (Verger et al., 2018)	2018	Retrospective cohort study	90 patients with newly diagnosed and untreated gliomas	Static and Dynamic 18F–FET PET	Characterization of gliomas based on IDH mutation and 1p/19q status	TBRmean showed best diagnostic performance for distinguishing IDH-mutated astrocytomas from IDH wild-type glioblastomas (cut-off 1.95; Sensitivity 89%, Specificity 67%, Accuracy 81%).	18F–FET PET parameters may help determine IDH mutation status, but cannot distinguish between IDH mutated, 1p/19q co-deleted oligodendrogliomas and other gliomas.
Bashir, A. et al. (Bashir et al., 2018)	2018	Retrospective cohort study	42 patients with histologically verified low-grade glioma (LGG)	O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET	Detection of malignant transformation, TBRmax, TAC, TTP, molecular biomarkers	Combining FET PET parameters (TBRmax > 1.6, TAC plateau/decreasing, TTP < 25 min) showed 93% sensitivity and 100% specificity (p = 0.001) when excluding oligodendroglial subgroup and prior treatment.	FET PET alone is not sufficient to replace histological confirmation but may help identify active tumor areas and assess tumor biology in some LGGs.
Vomacka, L. et al. (Vomacka et al., 2018)	2018	Retrospective cohort study	162 patients with newly diagnosed gliomas	Dynamic 18F-FET PET	Glioma grading, voxel-wise analysis, TTP, Slope, TBR5–15, TBR20–40	Voxel-based analysis yielded significant differences in parameters (e.g., TTP, Slope15–40, TBR) between WHO grades and IDH mutation status, showing better performance than traditional VOI-based methods.	Voxel-wise dynamic 18F-FET PET analysis enhances glioma characterization and may guide therapy by identifying aggressive sub-volumes.
Aprile, I. et al. (Aprile et al., 2015)	2015	Comparative Evaluation	49 patients with cerebral gliomas	MR Perfusion Imaging (CBV, PSR)	Glioma differentiation, CBV, PSR	Significant differences were found between low-grade and high-grade gliomas using CBV and PSR, with PSR showing better sensitivity and specificity, especially for distinguishing low-grade from grade III.	PSR evaluation is more effective than CBV in determining glioma grade and should be considered in MR evaluation of gliomas.
Takano, K. et al. (Takano et al., 2016)	2016	Retrospective cohort study	35 newly diagnosed, histologically confirmed nonenhancing gliomas (23 grade II, 12 grade III)	11C-Methionine PET, FDG-PET, Diffusion Tensor Imaging	WHO grading, Prognostic capability, Tumor-to-normal tissue ratio, ADC, FA	11C-methionine PET: Higher tumor-to-normal tissue ratios in grade III gliomas (P = .013, P = .0017). Maximum tumor-to-normal ratio > 2.0 predicted poorer PFS (P = .0044).	11C-methionine PET is valuable for WHO grading and prognosis in nonenhancing gliomas.
Song, P.J. et al. (Song et al., 2016)	2016	Comparative Evaluation	70 patients diagnosed with primary or suspected glioma	18F-FDG PET-CT, MRI	Glioma identification and grading, SUV, SUVcorrect, L/WM	PET-CT showed higher sensitivity, specificity, and accuracy than MRI (P < 0.05). Significant correlation between SUV, SUVcorrect, L/WM and glioma grade (P < 0.05).	18F-FDG PET-CT is superior to MRI in diagnosing and grading gliomas.
Yamashita, K. et al. (Yamashita et al., 2016)	2016	Retrospective cohort study	50 patients (17 with PCNSL, 33 with GBM)	IVIM-MR Imaging, 18F-FDG PET	Differentiation between PCNSL and GBM, fmax, Dmin, SUVmax	GBM had higher fmax, Dmin values, and lower SUVmax than PCNSL (P < 0.01, P < 0.0001, P < 0.0005, respectively). Combined fmax and Dmin improved diagnostic performance (AUC = 0.936).	IVIM-MR imaging provides useful quantitative data for distinguishing between PCNSL and GBM, with enhanced performance when combined with fmax and Dmin.
Nakajima, S. et al. (Nakajima et al., 2015)	2014	Retrospective cohort study	23 glioblastomas, 11 PCNSLs	DSC-PWI, DWI, 18F-FDG PET	Differentiation of PCNSL and glioblastoma, CBV ratio, ADC5%, SUVmax	Uncorrected CBV ratio, SUVmax, and ADC5% were highly effective in differentiating PCNSL from glioblastoma.	Uncorrected CBV ratio has high diagnostic performance comparable to SUVmax in differentiating PCNSL from glioblastoma.
Valentini, M.C. et al. (Valentini et al., 2017)	2017	Comparative Evaluation	12 glioblastoma patients, 48 biopsy specimens	Conventional and advanced MRI, 18F-FDG PET/CT	Tumor infiltration, Malignant tumor phenotype, SUVmax, rCBV, Cho/Cr, Cho/NAA, LL, ADC, FA	Highest SUVmax, rCBV, Cho/Cr, and Cho/NAA ratios were found in contrast-enhancing regions, corresponding to the most malignant tumor phenotypes. ADC and FA were variable.	Combined MRI and 18F-FDG PET/CT effectively recognize the biological significance of different glioblastoma areas, especially for tumor infiltration.
Sakata, A. et al. (Sakata et al., 2018)	2018	Retrospective cohort study	49 newly diagnosed glioma patients	Amide Proton Transfer Imaging, 18F-FDG PET, DWI	Glioma grading, Tumor-to-normal ratio, Minimum ADC, Mean amide proton transfer	Tumor-to-normal ratio, minimum ADC, and mean amide proton transfer had comparable accuracy in differentiating high-grade from low-grade gliomas. Combining amide proton transfer with FDG-PET improved diagnostic power.	Addition of amide proton transfer imaging to FDG-PET/CT enhances differentiation of high-grade from low-grade gliomas.

Source: Authors' development.

Table 1: Quality assessment of the reviewed studies by New Castle Ottawa Scale

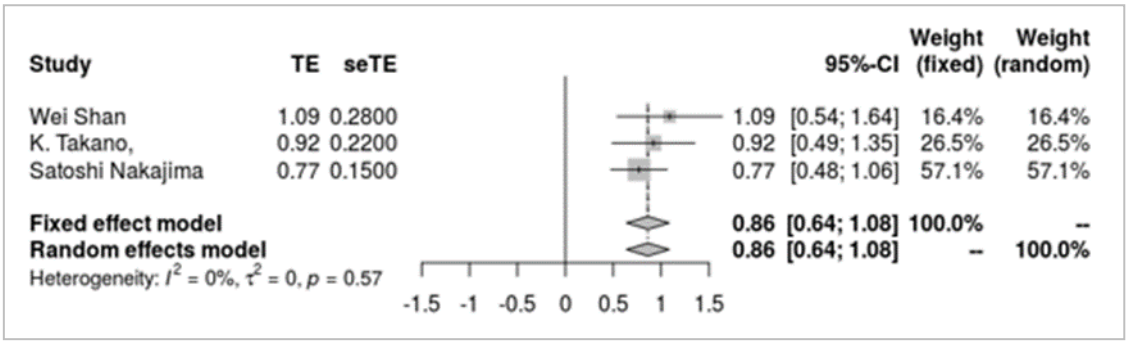
Study	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Compare ability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow-up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)	Representativeness of the exposed cohort (1)
Freitag, M.T. et al.	1	1	1		2	1	1	1	1
Jin, Y. et al.	1	1	1	1	2	1	1	1	1
Shan, W. et al.	1	1	1		2	1	1	1	1
Shaw, T.B. et al.	1		1		1	1	1	1	1
Roelcke, U. et al.	1		1		1	1	1	1	1
Verger, A. et al.	1	1	1		2	1	1	1	1
Bashir, A. et al.	1	1	1	1	2	1	1	1	1
Vomacka, L. et al.	1	1	1		2	1	1	1	1
Takano, K. et al.	1	1	1	1	1	1	1	1	1
Yamashita, K. et al.	1		1	1	1	1	1	1	1
Nakajima, S. et al.	1	1	1	1	2	1	1	1	1
Sakata, A. et al.	1	1	1	1	2	1	1	1	1

Source: Authors' development based on Lo et al., (2014).

Meta-analysis

The meta-analysis of three studies evaluating the use of the Apparent Diffusion Coefficient (ADC) in gliomas demonstrated a combined effect size of 0.8622, with a 95% Confidence Interval (CI) ranging from 0.6401 to 1.0843, indicating a moderate to high diagnostic value for ADC. Both fixed and random effects models showed similar effect sizes (0.8622), with a z-value of 7.61 and a p-value less than 0.0001, signifying strong statistical significance. The analysis revealed no significant heterogeneity among the studies, with a tau-squared (τ^2) value of 0, a H statistic of 1.00 (95% CI [1.00; 2.31]), and an I^2 statistic of 0.0% (95% CI [0.0%; 81.2%]), suggesting consistent findings across studies. The Q statistic of 1.11 with 2 degrees of freedom and a p-value of 0.5744 further confirmed the absence of significant variability. Overall, the results affirm ADC's reliability as an imaging biomarker for glioma detection and characterization.

Figure 2. Forest PLOT



Source: Authors' development

Discussion

This meta-analysis and systematic review demonstrate how imaging methods have advanced, enabling the early diagnosis and characterization of gliomas. Together, the data highlight the growing importance of sophisticated imaging modalities, including advanced Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Diffusion Tensor Imaging (DTI), each of which offers a distinct diagnostic benefit for glioma evaluation. Due to its special capacity to use non-invasive pictures to show information on tissue cellularity, microstructures, and microvasculature, DTI is being studied more and more for cancer diagnosis and treatment response prediction (Park et al., 2014). DTI may be used to create a variety of feature maps that quantify variations in various diffusion parameters. For instance, whereas MD shows the general diffusion qualities, FA denotes the directionality or degree of diffusion anisotropy. While RD takes into consideration the diffusion in the other two directions that are perpendicular to the primary direction, AD characterizes the diffusion qualities along a specific direction (the principal axis) (Jin et al., 2020).

The research conducted by Jin et al. (2016) and Freitag et al. (2016) agrees that DTI may identify abnormal glioma alterations far earlier than traditional imaging methods. AUC of 0.96 further verified the outstanding diagnostic accuracy of Apparent Diffusion (AD) maps in DTI, according to Freitag et al., with a sensitivity of 94.94% and specificity of 89.7% in identifying malignant transformation (MT) in WHO II low-grade gliomas. According to Jin et al (2016), which support these findings, glioblastoma recurrence may be identified up to two months prior to the onset of clinical symptoms. These measures, such as Fractional Anisotropy (FA) and Neurite Density Index (NDI), are effective in detecting these alterations.

About the differentiation of various tumor grades in particular, this body of data establishes DTI as an essential tool for the accurate and timely identification of glioma progression and recurrence.

18F-FDG PET considerably improves the overall diagnostic accuracy and specificity for glioma characterization, as the reviewed studies show, particularly when paired with MRI. Good evidence for the use of PET in glioma assessment can be found in the works of Shaw et al. (2019) and Roelcke et al. (2016). High-grade gliomas could be identified with 100% specificity when FDG-PET/CT was combined with MRI, as shown by Shaw et al. This finding highlights the complementing role that PET plays in improving diagnostic accuracy. Similar findings were made by Roelcke et al., who discovered that Amino Acid PET provided more accurate progression-free survival (PFS) estimates when used to track treatment response in WHO grade II gliomas than did MRI. When combined with MRI, PET's diagnostic utility is much increased, as seen by the results of these studies. This is especially true for differentiating between glioma grades and tracking the effectiveness of therapy. The findings are consistent with a study conducted by Quartuccio et al (2020) which found that the combination of 18F-FDG PET and MRI gives supplementary information that improves glioma management by improving diagnostic accuracy, prognosis prediction, treatment planning, and recurrence assessment (Quartuccio et al., 2020).

Glioma imaging still relies heavily on MRI, but advances in perfusion imaging and its combination with other modalities, like as PET, have improved its diagnostic potential even more. The significance of MR perfusion imaging and related parameters, such as Cerebral Blood Volume (CBV) and Perfusion-Sensitive Ratio (PSR), in distinguishing between glioma grades is highlighted by Aprile et al. (2015) and Valentini et al. (2017). All of these studies point to PSR as having greater sensitivity and specificity in identifying low-grade gliomas from higher-grade gliomas. According to Vomacka et al. (2018) and Sakata et al. (2018), the combination of PET with conventional and advanced MRI offers even more insights on tumor biology and grade, hence bolstering the significance of advanced MRI methods in thorough glioma assessment. It is consistent with a previous study by Chung et al. (2015) that highlighted how improvements in diffusion-weighted imaging and multiparametric MRI and PET imaging, along with the use of tracers like methyl-11C-l-methionine, have improved the capacity to noninvasively assess glioma grade and molecular characteristics, guiding customized treatment approaches (Chung et al., 2015).

The diagnostic usefulness of ADC as an imaging biomarker for gliomas is confirmed by the meta-analysis carried out for this study. The dependability of ADC in differentiating between various glioma grades is confirmed by the overall effect size of 0.8622, which demonstrates substantial statistical significance ($p < 0.0001$) and no significant heterogeneity across the trials. This strengthens the usefulness of ADC in standard clinical practice by confirming its position as a dependable and consistent indicator across several investigations. The combined data from this systematic review and meta-analysis highlights how glioma imaging is changing. New methods like magnetic resonance imaging (MRI), PET, and diffusion tensor imaging (DTI) are improving early detection while also offering vital information about the biology and grade of the tumor. Combining these techniques, especially MRI and PET, provides a more thorough method of characterizing gliomas and may result in more individualized and successful treatment plans.

Limitations and future research

It's important to take into account a few restrictions. Because most of the included studies were retrospective in nature, there may be selection bias and a restriction to how broadly the results may be applied. The variability seen in imaging techniques, patient groups, and tumor subtypes across studies presents obstacles to the standardization of imaging criteria, which may affect the repeatability of findings. Furthermore, some research's dependence on tiny sample sizes reduces the statistical power and validity of the results reached. The broad use of modern imaging modalities, such as DTI and PET, may be limited by the uneven accessibility and availability of these tools in clinical settings. Larger, multicenter studies should be the main focus of future research to confirm results and standardize imaging procedures. AI integration and the combination of imaging and genetic profiling may improve glioma diagnosis and outcomes while also improving accuracy and therapy.

FINAL REMARKS

The substantial developments in imaging methods for the early identification and characterization of gliomas are highlighted by this systematic review and meta-analysis. Among the modalities evaluated, PET (especially with amino acid tracers) and DTI (diffusion tensor imaging) have shown a great deal of success in glioma grade differentiation and tumor biology assessment. Perfusion and spectral imaging are two advanced MRI methods that improve glioma characterization and provide important information for treatment planning. The Apparent Diffusion Coefficient (ADC) is a strong indicator in glioma imaging, and the meta-analysis confirms this. All things considered, the combination of these cutting-edge imaging modalities leads to enhanced diagnostic precision and a deeper comprehension of glioma pathophysiology, which in turn informs individualized treatment plans.

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Contribution of each author to the manuscript:

	% of contribution of each author				
Task	**A1**	**A2**	**A3**	**A4**	**A5**
A. theoretical and conceptual foundations and problematization:	20%	20%	20%	20%	20%
B. data research and statistical analysis:	20%	20%	20%	20%	20%
C. elaboration of figures and tables:	20%	20%	20%	20%	20%
D. drafting, reviewing and writing of the text:	20%	20%	20%	20%	20%
E. selection of bibliographical references	20%	20%	20%	20%	20%
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