A Systematic Review of Screening Techniques for Early Detection of Metastatic Brain Tumors and their Histopathological Correlation

[1] Souvik Mazumder; [2] Sanjay Nag; [3] Prasenjit Kundu; [4] Sayani Ghosh
[1,4] Research Scholar, [2,3] Associate Professor
[1,2] Swami Vivekananda University, Barrack pore, India
[3,4] Institute of Engineering and Management, University of Engineering and Management, Kolkata, India

Corresponding Author: Souvik Mazumder

Abstract: This systematic review assesses and analyzes the imaging-based screening methods and histopathological correlations that are available for the early detection of metastatic brain tumors. It reviews the critical role that MRI and CT play as primary diagnostic tools, while advanced modalities like PET-MRI, MRS, and DTI help in tumor characterization, metabolic profiling, and treatment surveillance. The integration of artificial intelligence and machine learning has greatly enhanced image segmentation accuracy, classification precision, and survival prediction but still suffers from limitations related to dataset dependency, computational complexity, lack of interpretability, and clinical validation. The histopathological examination is considered the gold standard since it provides crucial information on tumor origin as well as immunohistochemistry molecular subtype and prognostic markers through genomic profiling. Radio genomics trends are emerging more prominently with biomarker analytics to highlight how close imaging is converging with molecular diagnostics toward precision medicine in neuro-oncology. By looking at literature between 2020-2025 this review brings out existing research gaps and stresses the importance of multimodal frameworks driven by AI integrating imaging pathology plus molecular data for better early detection as well as personalized treatment concerning metastatic brain tumors.

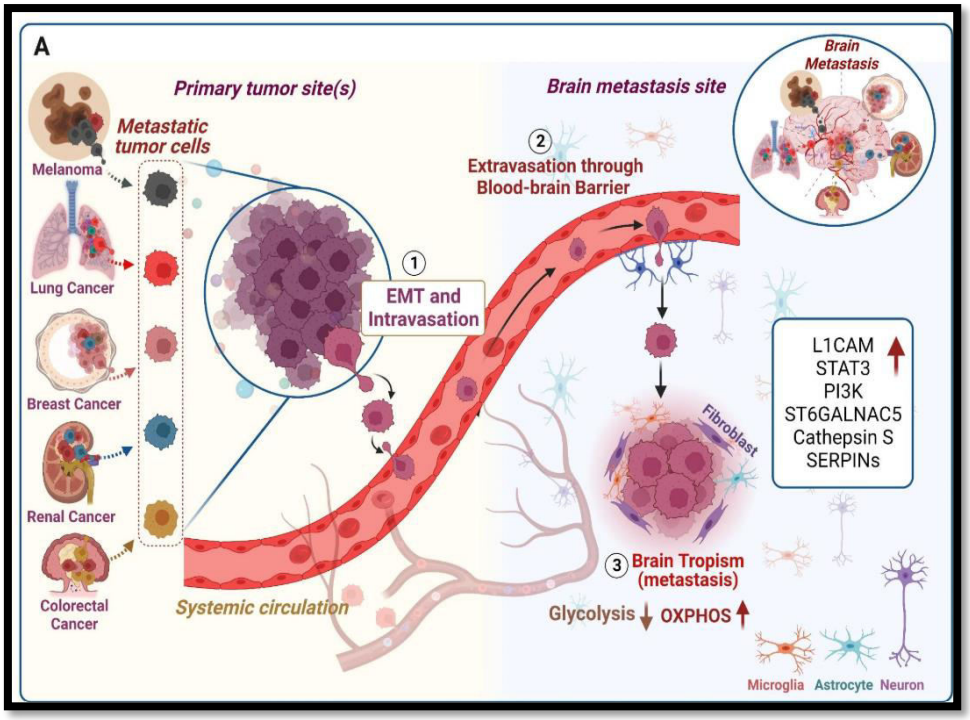
Keywords: MRI, CT, Metastatic Brain Tumors, Artificial Intelligence, Histopathological Correlation

1. Introduction

Brain metastases are the most tragic and fatal systemic manifestations of cancer, which rank among the top causes of death worldwide [1, 2]. These are the tumors that

result from cancer cells that have spread to the brain through the blood vessels, and therefore, the secondary tumors are found in the brain tissue, the meninges, or the ventricles. In adults, brain metastasis exceeds primary brain tumors once in every four cases [3]. As the incidence of cancer rises across the globe, the incidence of brain metastases too has increased, stemming from several factors: improved control of the systemic cancer, prolonged overall survival, and improved imaging modalities that are more sensitive leading to earlier detection of the metastases [4]. These advancements allow patients to live longer with their primary disease, giving metastatic cells more time to spread to the brain and be identified through advanced diagnostic imaging. Many interventions aimed at assisting patients or interrogating prognostic course requires earlier diagnosis of these lesions [5].

Human brain is the preferred site where metastatic cells grow as a result of the primary cancers that have their origin in the lung, breast, melanoma, renal, and colorectal origin due to the unique vascular structures and microenvironment in the brain [6, 7]. Metastatic tumors when developed may lead to a devastating neurological impairment, cognitive dysfunction, seizure and increased intracranial pressure leading to a significant impairment of the quality of life of the patient [8]. Nonetheless, Brain tumors going metastasis will spread elsewhere in the body. Therefore, efficient screening and correlation with the results of histopathological examination are the essential elements of multidisciplinary oncologic care. The interdisciplinary approach involving radiology, oncology, and pathology has turned out to be the key to the diagnostic accuracy and treatment planning on a case-by-case basis [9].



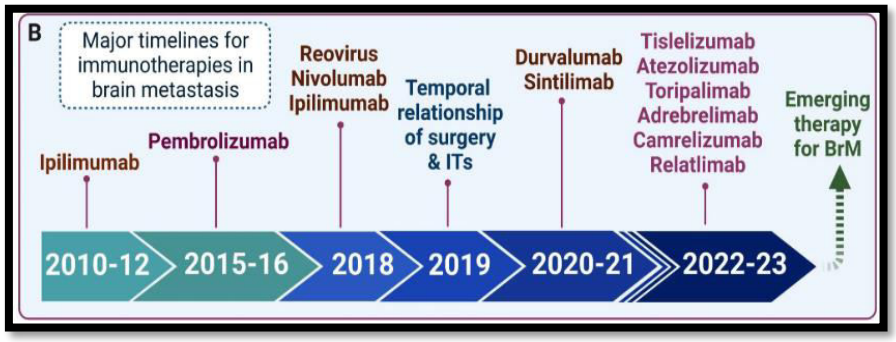


Figure 1: (a) Mechanism of brain metastasis and (b) the timeline for progress in early detection and immunotherapy [10]

Over the past two decades, these neuroimaging and computational methods have undergone massive developments that have completely transformed the detection and characterization of brain metastases. As basic tools of screening, conventional imaging methods remain the most in use, such as computed tomography (CT) [11] and magnetic resonance imaging (MRI) [12], while recent modalities include positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and advanced diffusion tensor imaging (DTI) that yield functional and metabolic information [13].

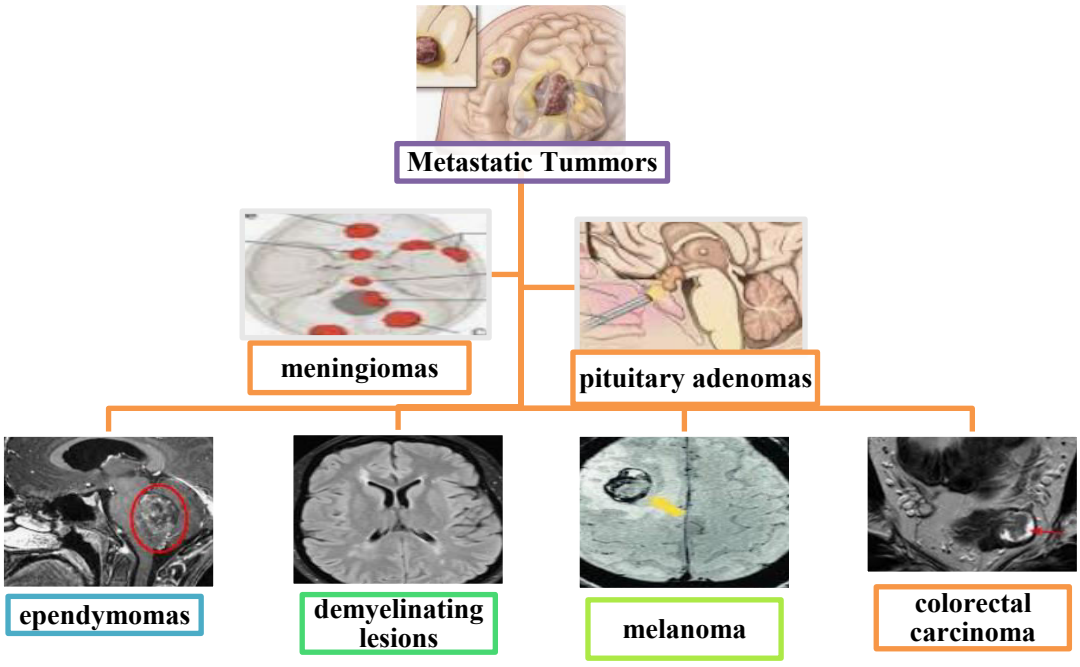


Figure 2: Types of metastatic brain tumour

Apart from the aspect of the early locating of lesions, these imaging modalities are also very important in the differential diagnosis of metastasis from other intracranial disorders like primary glioma lesions, an abscess, as well as demyelinising lesions (figure 2). After these technological achievements, histopathological examination remains the gold standard of a definitive diagnosis where it provides the

vital information of tumor type, grade, and Cellular specifications [14]. The relationship between the imaging results and histopathology analysis helps to diagniosis between the radiological suspicion and diagnostic confirmation, ensuring that the tumor is classified correctly and that the result would give a way to administer targeted therapies.

1.1 Screening and Imaging Modalities for Early Detection

The detection of metastatic brain tumors at an early stage relies on screening tools that are sensitive and specific enough to detect small lesions even before there are neurological problems [15]. Of the available modalities, magnetic resonance imaging (MRI) is presently the most sensitive and non-invasive modality for detecting brain metastases. MRI's superior contrast for soft tissues and ability to visualize in multiple planes allows for lesions as small as 2-3 mm being detected [16]. Using enhanced MRI will further increase the detection sensitivity of metastases by demonstrating the areas of blood-brain barrier impairment, which is one of the first signs of metastatic involvement. The use of advanced MRI techniques, such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have expanded diagnostic sensitivity by demonstrating tumor cellularity and vascularity, respectively [17]. Diffusion-weighted imaging is useful for differentiating cystic or necrotic metastases from abscesses, and perfusion-weighted imaging is useful for the assessment of angiogenesis and micro vascular proliferation, both of which are important for detecting malignant transformation.

Computed tomography (CT), has sensitivity that is lower than MRI, although it is used extensively in the primary examination, particularly in cases of emergency. It is also quick and therefore convenient to patients with contraindications to MRI and those in urgent need of investigation. Contrast enhancement can also outline various metastases, calcifications, and hemorrhagic elements which would not be visible on a regular scan [18]. Whole-brain MRI screening being conducted regularly is a common practice in patients with established systemic malignancies to identify asymptomatic metastases.

Addition of functional imaging modalities has also contributed to early diagnostic abilities. Metabolic and cellular characterization of brain lesions can be performed using positron emission tomography (PET) and particularly by using combination of CT with PET (PET-CT) or MRI with PET (PET-MRI) [19]. The 18F-fluorodeoxyglucose (FDG) being the most frequently used tracer demonstrates foci of higher glucose rates being affiliated with viable tumor growth [20]. But due to the high background uptake in normal brain tissue, new tracers are in use that delineate the tumor better into 18F-FDOPA and 11C-methionine. These tracers use the amino acid transport systems, which is amplified in the metastatic lesions, and, therefore, enhances specificity [21].

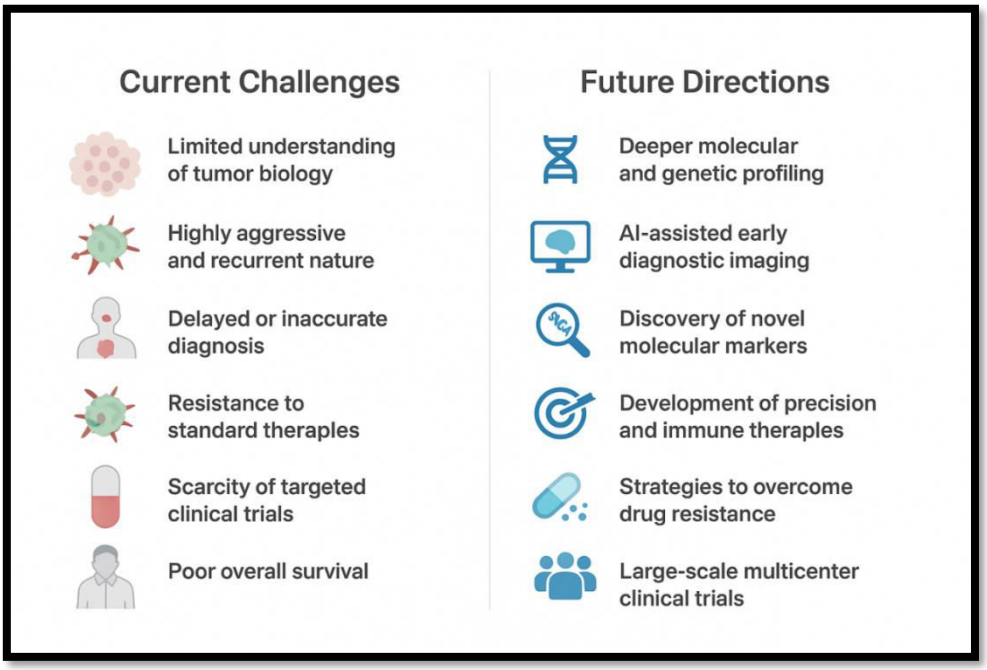


Figure 3: Brain metastatic challenges and future direction

Modern imaging techniques, like magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI), serve to add new layers of diagnostic information. MRS provides the ability to measure biochemical markers, such as choline, creatine, and N-acetylaspartate, providing non-invasive metabolic profiling, there is potential to help differentiate metastatic tumors from primary glioma and other intracranial pathology [22]. DTI enables more information with the ability to map white matter tracts, which facilitates surgical planning and increases our understanding of the infiltrative behavior of metastatic cells.

In the last couple of years, deep learning and machine learning algorithms have been implemented in medical imaging, which enabled the detection, segmentation, and classification of lesions automatically [23]. Deep learning-trained systems on large datasets of imaging are able to detect metastatic brain tumors at an early stage. Moreover, radiomics-a newly developed domain based on high-level phenomena of medical images-have shown the potential for tumor origin prediction, cell subtype, and treatment response [24]. New technologies are establishing the path for more specific diagnostics whereby clinicians identify metastases at an earlier phase of the disease and make more effective interventions.

1.2 Histopathological Correlation and Diagnostic Validation

Even though imaging plays an essential role in the non-invasive detection of metastatic brain tumours, histopathological examination remains the gold standard for confirming the diagnosis as well as for determining tumor biological behaviour (such as metastasis, invasion, cell proliferation, genomic instability, etc.) [25]. Histopathology reveals the cellular framework, morphologic features, and cellular markets that are not even indirectly seen by imaging studies. Usually,

histopathological examination involves stereotactic biopsy or surgical resection of the tissue followed by microscopic examination of stained sections. Standard brain tumor histopathological examination is accomplished by Hematoxylin and Eosin staining (H&E) staining for simple cellular morphology, and/or Immunohistochemistry (IHC) to detect tissue-specific antigens serving as the primary origin of the tumor[26].

Figure 4: Schematic representation illustrating key components and processes involved in histopathological correlation for brain tumor diagnosis and analysis.

The correlation of histopathology is very important in making an accurate diagnosis, especially when the imaging results are not clear or even contradictory. For instance, the lesions that enhance with a ring on MR imaging may be metastases, abscesses, or demyelination, thus a cellular study is required to arrive at a certain diagnosis of the cancerous nature, as in the case of the original source [27] (figure 4). The brain tumors due to metastasis often have features that are akin to the original tumors, such as glandular characteristics in adenocarcinomas, melanin in melanomas, or clear cytoplasm in renal cell carcinomas. The identification of these structures is helpful when differentiation between primary central nervous system (CNS) tumors and metastatic cases, which is very critical regarding the choice of treatment, is done [28].

Histopathological correlation in metastatic brain tumors is important for diagnosis confirmation and primary origin determination of the malignancy. It includes microscopic examination of tissue sections with H&E staining to assess cellular morphology, plus IHC for tumor-specific antigens [29] identification. These methods help differentiate metastatic lesions from primary brain tumors and other mimicking pathologies. Molecular and genetic profiling can further assist in characterizing subtype, predicting prognosis, and guiding targeted therapy [30, 31]. Therefore, histopathological correlation is a crucial link between imaging, molecular analysis as well as clinical evaluation needed for accurate diagnosis plus personalized treatment planning in patients with metastatic brain tumors.

This review aims at a critique and comparison of various screening techniques and images applied in the early discovery of metastatic brain tumors. This study critically appraises

- existing literature with regard to the diagnostic performance, accuracy, and clinical reliability of MRI, CT, and PET imaging modalities
- their correlation with histopathological findings, and
- explores the role of artificial intelligence
- radiomics in enhancing early detection, classification, and prognostic assessment of brain metastases.

The structure of this paper is as follows: Section 2 describes the research methodology, Section 3 outlines the literature survey, Section 4 discusses the key findings, limitations, and gaps in research, and Section 5 concludes with future perspectives in neuro-oncological diagnostics.

2. Review Methodology

In this part, information is presented on the process and selection criteria that were used to select relevant papers for this review.

2.1 Search Strategy

The main goal of this Systematic Literature Review (SLR), was to investigate and examine the current methods and alternative approaches that are available in the screening of metastatic brain tumor early on and through confirmatory methods of the histopathology. Advanced searches were performed on established databases on science i.e. PubMed, IEEE Xplore, Scopus, Science Direct, Springer Link and Web of Science to locate the studies. The review was aimed at locating previous studies covering diagnostic methods of imaging, histopathological validation, and clinical correlations of neuro-oncology. To be used was a broad-based search in the form of a keyword search strategy focusing on keywords that can be found in the titles, abstracts, and subject areas when it comes to brain metastasis screening and diagnostic accuracy. There were no limitations set on the publication year so that both classical and contemporary studies are included. Only the academic publications, including research papers, conference papers, and reviews were taken into consideration. Table 1 presents the research questions used in this review and Table 2 displays a detailed list of search terms applied

Table 1: Research questions formulated for the systematic review

Sr. No.	Research Question
1.	What are the most effective imaging and screening techniques for early detection of metastatic brain tumors?
2.	How do advanced neuroimaging modalities (such as MRI, CT, and PET) contribute to improving diagnostic accuracy in metastatic brain tumors?
3.	What is the role of imagein validating imaging-based diagnoses of metastatic brain lesions?
4.	How can emerging technologies, including AI and radiomics, enhance early detection and classification of metastatic brain tumors?
5.	What challenges and limitations exist in integrating imaging for comprehensive tumor assessment?

The table 2 and figure 5summarizes the literature search results for the systematic review, highlighting the number of research papers extracted under different keyword categories related to metastatic brain tumor detection. A total of **892 papers** were identified, with the highest number focusing on **metastatic brain tumor detection (210)** and **neuroimaging modalities (188)**, followed by studies on **early screening techniques (165)** and **histopathological correlation (142)**. Emerging areas such as **AI and machine learning applications (121)** and **radiomics-based image analysis (66)** also contributed significantly, reflecting growing interest in advanced diagnostic technologies.

Table 2: Total number of papers retrieved for each keyword

List of Searched Keywords	Papers Extracted
Metastatic Brain Tumor Detection	210
Early Screening Techniques	165
Neuroimaging Modalities (MRI, CT, PET)	188
Histopathological Correlation	142
AI and Machine Learning in Brain Tumor Diagnosis	121
Radiomics and Image Analysis	66
Total	**892**

A total of 892 papers were retrieved via the use of various keywords (metastatic brain tumor detection, neuroimaging modalities, early screening techniques, histopathological correlation, AI and machine learning applications, and radiomics-based image analysis), and then inclusion and exclusion procedures were carried in which the Papers published between 2020 and 2025 were selected, while those published before 2020 were excluded.

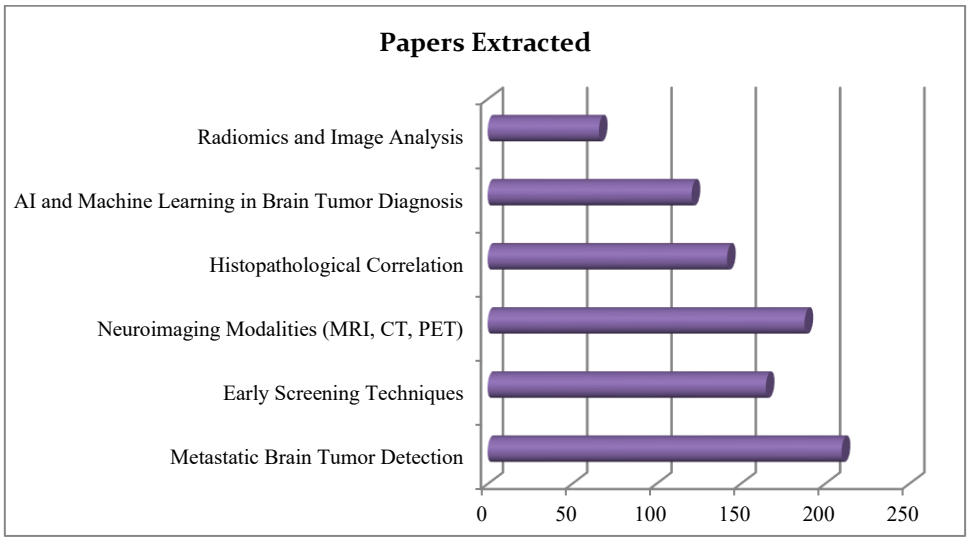


Figure 5: List of various Keywords

2.2 Scrutinizing of paper for study

This review used a multi-stage selection of primary studies. During the initial stage of selection, 2,335 records were retrieved from the leading scientific databases, PubMed, IEEE, Scopus, Web of Sciences, Science Direct and Springer. Subsequently, irrelevant and insignificant publications were discarded based on their titles and abstracts.. The remaining papers 892 were then inspected for Quality and relevance to the research question. Figure 6 shows the entire selection process which followed the PRISMA framework.

The review process is guided with laid down inclusion and exclusion criterion that is of paramount help in the selection of quality research articles. The inclusion and exclusion criteria for the literature search are as follows:

- Research publications published from 2020 to 2025 are eligible for inclusion in the review for the multiple database (IEEE, web of science, scopuspubmed etc),
- Excluding the document other than articlsuch as conference paper, conference review, review, book chapter, etc
- Only journal articles are included; conference papers, books, and other document types are excluded because in systematic paper the goal is to collect high quality, original, peer-reviewed evidence.
- Articles that are not in the English language are excluded to maintain consistency and relevance.

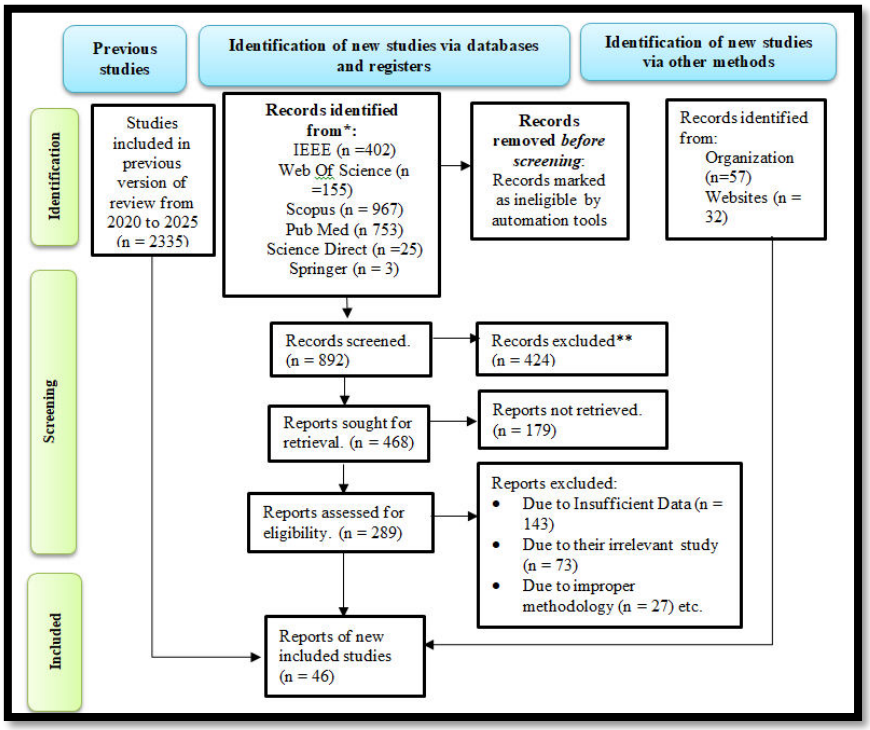


Figure 6: A PRISMA-based flowchart for systematic reviews of publications found in databases.

Table 3: The criteria for determining what is Included and Excluded

Criterion	Inclusion	Exclusion
Keywords	Records conferring the relationship (such as Metastasis Brain tumor, MRI, CT scan, Histopathological Correlation, AI etc)	Records excluded where variables exhibit no correlation
Document Type	Article	Conference paper, Erratum, conference review, book chapter and Review
Source Type	Journals	Book series, book, and chapter in book.
Language	English	Other than English
Timeframe	Concerning 2020-2025	<2020
Category	Open Access	Paid Access

The PRISMA layout below demonstrates the systematic approach taken to identify, screen, and include studies in the review, from 2020 to 2025 (figure 5). Initially, the review considered 2,335 studies from2020 to 2025. New records came from various databases and registers, specifically IEEE (n=402), Web of Science (n=155), Scopus (n=967), PubMed (n=753), Science Direct (n=25), and Springer (n=3), and records from organizations (n=57) and websites (n=32).

Many reports were excluded on account of inadequate data presentation, n = 143; irrelevant to the study objectives, n = 73; improper methodology, n = 27. A total of 46 studies satisfied all the criteria and could be included into the final systematic review. The PRISMA model allows for transparency in the selection process to ensure methodological rigor and reproducibility. It illustrates the systematic filtering of the literature throughout the process, from identification to inclusion, where careful evaluation and exclusion of unsuitable studies have taken place.

2.3 Demography of publication

Figure 7 captures a distribution overview of the 46 research studies that made it to this systematic review annually. It has a steady growth trend between 2020 and 2022, which indicates the growing curiosity of early screening and diagnostics of metastatic brain tumors. The highest level was attained in 2022 with 10 studies that showed a greater exploration of AI-assisted imaging and histopathological validation methods. Since then, the number marginally declined, but between 2022 and 2025, the active work on the topic was also performed with the emphasis on the perennial significance of the combination of imaging technologies with pathological examination to be conducted to achieve the early and correct diagnosis.

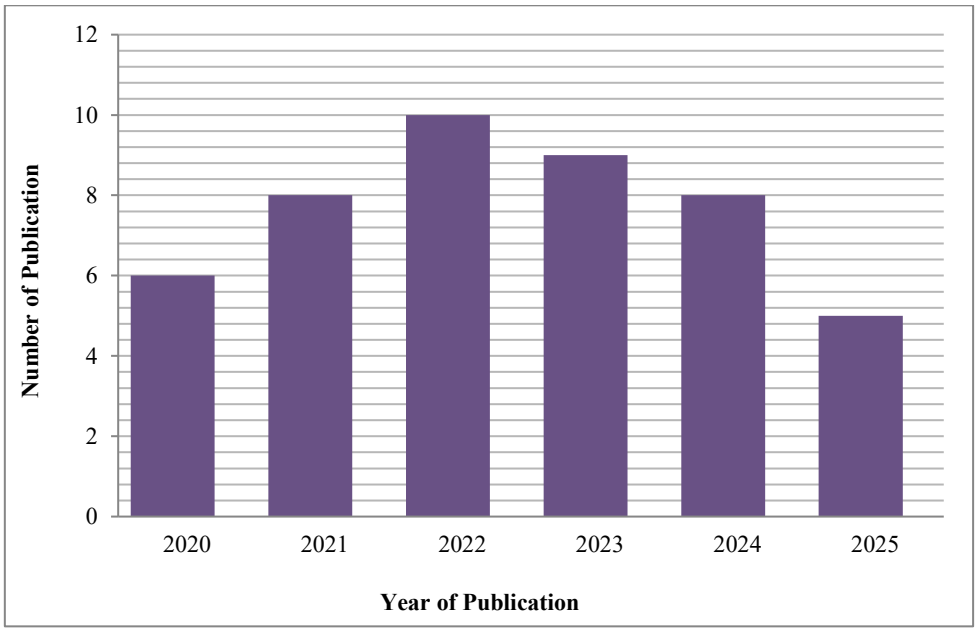


Figure 7: Annual distribution of selected studies (2020–2025)

3. Literature Analysis

Imaging-Based Screening Techniques for Early Detection of Metastatic Brain Tumors: MRI and CT Modalities

Imaging technologies have long played a pivotal role in the early detection and characterization of metastatic brain tumors, with modalities like Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) forming the diagnostic cornerstone. Fatima et al. (2025) [32] emphasized that conventional MRI and CT enable structural

identification, while advanced MRI techniques, such as diffusion-weighted and chemical-based imaging, allow for the detection of metabolic alterations within tumors. Abbasi et al. (2025) [33] looked at the complementary ability of fusion imaging, more specifically PET/MRI, which gave views into glioblastoma multiforme (GBM) aggressiveness and how it responds to treatment. Likewise, Keck et al. (2025) [34] showed the use of MRI for tracking embryonal tumors with PLAGL amplifications over time; they noted different radiological patterns that matched up with survival outcomes. Roy et al. (2025) [35] added to multimodal diagnostics by bringing together MRI, CT, and molecular-level imaging like MRS and fMRI for more exact tumor characterization. Gallegos et al. (2025) [36] pointed out conventional MRI and PET's limitations in telling apart tumor progression from effects induced by immunotherapy which led to checking quantitative MRI and PET biomarkers for early therapy monitoring. In pediatric oncology Nikam et al. (2022) [37] discussed advanced MRI sequences' importance MR spectroscopy perfusion imaging elastography in complementing CT and PET scans for detecting pediatric brain tumors more accurately. Kamepalli et al. (2023) [38] emphasized the need for standardized MRI protocols including T1W T2W FLAIR DWI sequences to help with differential diagnosis tumor grading and treatment planning. Also, Madamesila et al. (2023) used longitudinal diffusion imaging plus radiomic analysis from both MR and CT data to find metastases several months before they showed up on contrast-enhanced scans achieving more than 87% accuracy in detection through machine learning classifiers such as XGBoost and Random Forest.

Table 4: Summary of Key Studies on Imaging-Based Screening Techniques for Early Detection of Metastatic Brain Tumors (2022–2025)

S.No	Author (Year)	Imaging / Model / Technique Used	Key Findings (Including Evaluation Metrics)	Clinical / Diagnostic Impact
1	**Fatima et al. (2025)**	MRI, CT, PET-CT, PET-MRI	Advanced MRI detects biochemical tumor changes; hybrid PET-MRI enhances early diagnosis; noted scan duration and metallic implant risks.	Improved diagnostic precision and treatment planning.
2	**Abbasi et al. (2025)**	PET-MRI Fusion, FLT-PET, MATLAB & imlook4d	PET-MRI integration improved GBM diagnosis; MRI showed significant survival-based variations ($p<0.04$); PET	Validated PET-MRI as superior tool for GBM monitoring.

			SUVmax, TLA trends not statistically significant.	
3	**Keck et al. (2025)**	MRI, Serial Imaging Analysis	Compared PLAGL1 vs PLAGL2 amplified embryonal tumors; progression-free survival varied (p=0.0055); PLAGL2 required intensive chemotherapy.	Suggested subtype-based treatment guided by imaging data.
4	**Roy et al. (2025)**	MRI, fMRI, MR Spectroscopy, CT	Integrated imaging with molecular profiling; AI-assisted tumor characterization; nanotechnology-based diagnostics emerging.	Promoted multimodal imaging for personalized therapy.
5	**Gallegos et al. (2025)**	Quantitative MRI, PET	Novel MRI/PET biomarkers to distinguish tumor progression vs. immunotherapy effects; early response stratification potential.	Enabled early differentiation of therapy response.
6	**Hussain et al. (2024)**	DL Models (CNN, RNN, GAN), Multimodal Imaging	Systematic review of DL for tumor detection; multimodal imaging improved classification accuracy; emphasized CNN-based PET-MRI/CT.	Showed AI's efficiency in multimodal tumor analysis.
7	**Chen et al. (2024)**	MRI Super-Resolution (SR) Algorithm	Enhanced MRI resolution via deep convolutional model; outperformed SOTA at 2× and 4× scaling in PSNR & SSIM.	Improved MRI quality aiding early clinical diagnosis.
8	**Kong et al. (2024)**	Multi-scale Feature Fusion (M3) on MRI	PCA + SVM classifier; improved glioma and metastases	Strengthened diagnostic precision using

			classification; validated with ablation studies.	attention mechanisms.
9	**Sarkar et al. (2024)**	VGG16 CNN on MRI Dataset	Transfer learning enhanced detection accuracy; effective in identifying tumor presence.	Reliable early diagnostic model improving neuroimaging workflow.
10	**Abdusalomov et al. (2023)**	YOLOv7 + CBAM + BiFPN on MRI	Achieved higher detection accuracy; improved feature extraction and multi-scale fusion; large dataset used.	Automated, precise multi-class tumor detection tool.
11	**Kamepalli et al. (2023)**	MRI (T1W, T2W, DWI, MR Perfusion)	Standardized MR protocol for diagnosis, grading, and follow-up; emphasized multidisciplinary coordination.	Enhanced MRI utility in diagnosis and post-treatment monitoring.
12	**Madamesila et al. (2023)**	Diffusion Imaging + Radiomics + ML (SVM, RF, XGBoost, AdaBoost)	Identified metastases before manifestation; accuracy up to 87.7% (training), 85.8% (validation); AUC ~0.91–0.92.	Enabled preclinical detection months earlier.
13	**Nikam et al. (2022)**	MRI, CT, PET, SPECT	Advanced MRI and PET imaging provided metabolic and structural data; radiomics predicted tumor subtypes.	Improved pediatric tumor diagnosis and prognostication.
14	**Kuestner et al. (2022)**	PET/MRI + CNN	37 melanoma patients; achieved 95% accuracy, 92% sensitivity, 96% specificity; CNN outperformed handcrafted features.	Provided precise risk stratification for metastases.
15	**Arabahmadi et al. (2022)**	CNN-based MRI Analysis	Reviewed DL applications for MRI-	Highlighted AI's transformative

			based brain tumor detection; identified challenges and future directions.	role in neuroimaging.
16	**Maqsood et al. (2022)**	Deep Neural Network + MobileNetV2 + M-SVM	Accuracy: 97.47–98.92% on BraTS&Figshare datasets; integrated explainable AI (XAI).	Delivered explainable and accurate tumor classification system.

Recent developments have further merged artificial intelligence and imaging analysis for better screening and classification results. Hussain et al. (2024) reviewed deep learning methods in multimodal imaging, particularly PET-MRI and PET-CT, which optimize tumor detection and classification by leveraging CNNs and attention-based models. Chen et al. contributed a super-resolution algorithm to improve MRI image quality and segmentation reliability for early detection. Kong et al. presented a mask-attention model with feature fusion for multi-parametric MRI classification that identifies gliomas and metastases effectively. Sarkar et al also used the VGG16 CNN architecture to prove accurate identification of brain tumors via MRI; this underlines its potential as a reliable diagnostic aid. Abdusalomov et al improved upon the YOLOv7 model by integrating attention mechanisms and spatial pyramid pooling which enhanced tumor localization on MRI images significantly. Kuestner validated a CNN-based PET/MRI diagnostic framework for metastasized melanoma with a 95% accuracy rate in risk stratification. Arabahmadi systematically reviewed CNN architectures applied to brain MRI, thus cementing deep learning as an integral part of early tumor detection. Finally, Maqsood proposed a hybrid deep neural network that amalgamated segmentation, transfer learning, and explainable AI to identify glioma, meningioma, and pituitary tumors with over 98% accuracy. Collectively these sixteen studies prove that the integration of MRI and CT imaging with advanced computational models significantly enhances the early detection diagnosis and monitoring of metastatic brain tumors supporting more effective personalized treatment strategies.

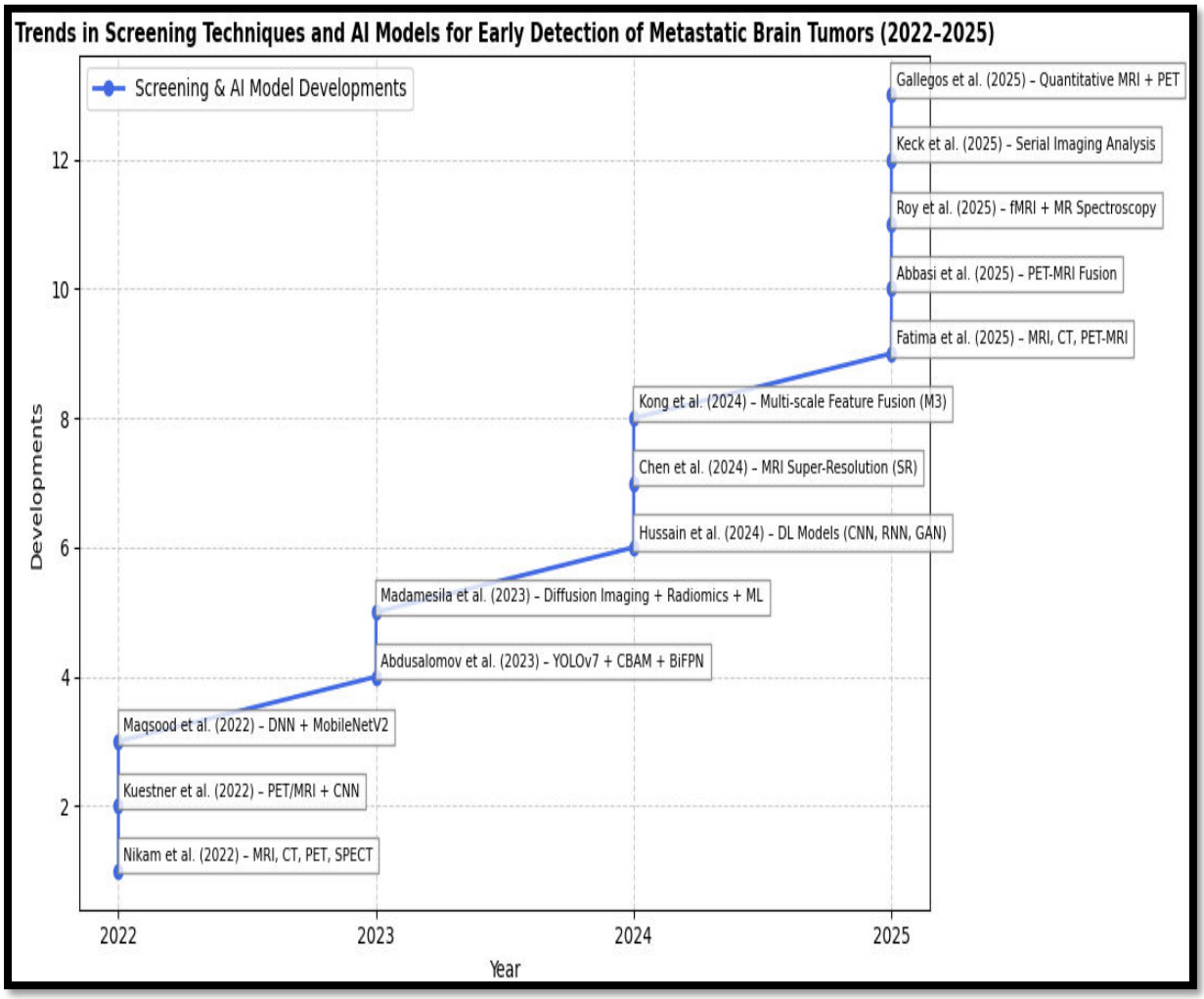


Figure 8: Trends in Screening Techniques and AI Models for Early Detection of Metastatic Brain Tumors (2022–2025)

The portrayal in figure 8 depicts a timeline of significant innovations in imaging and artificial intelligence techniques for the detection of metastatic brain tumors from 2022 to 2025. The timeline demonstrates the steady increase in research output and marks the important involvement of MRI, CT, PET, and AI-based multimodal systems. The first phase of investigations (2022–2023) was all about the combination of MRI, PET/MRI, and deep neural networks, while the second phase (2024–2025) was concerned with hybrid deep learning architectures, feature fusion, and quantitative MRI/PET biomarkers. The trend indicates the increasing collaboration between imaging and AI, which in turn has made a significant impact on neuro-oncology with regard to early diagnosis, tumor classification, and treatment planning.

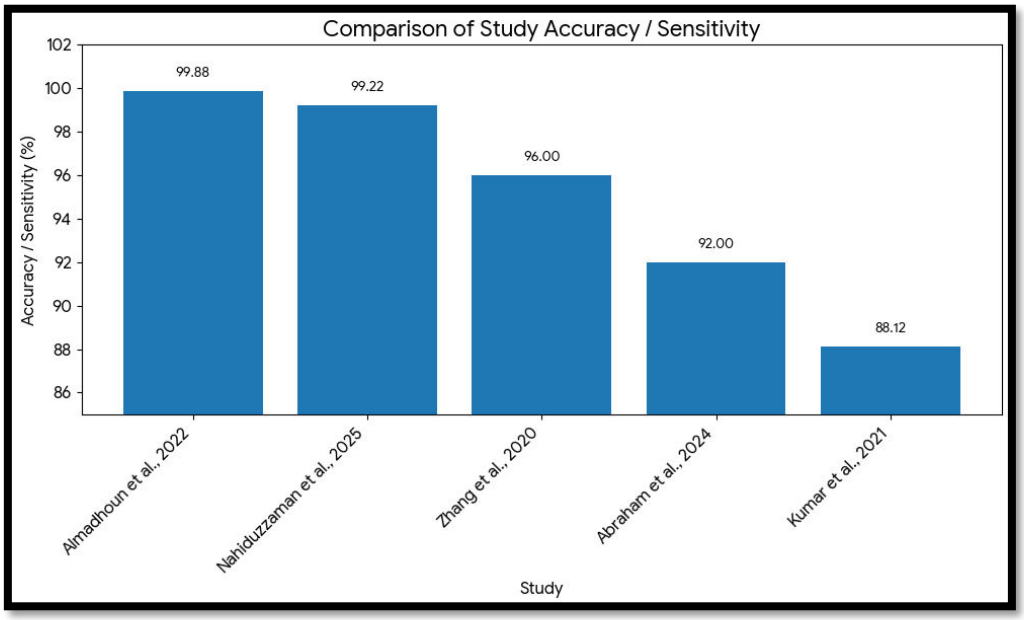


Figure 9: Comparison of Study Accuracy and Sensitivity in AI-Based Brain Tumor Detection (2020–2025)

This figure 9 presents a comparison of the accuracy and sensitivity values reported in five pivotal studies that used AI and machine learning methods for brain tumor detection between 2020 and 2025. Among the studies, Almadhoun et al. (2022) and Nahiduzzaman et al. (2025) are credited with the best performance, attaining accuracies of 99.88% and 99.22%, respectively, while Zhang et al. (2020) came next with a 96% accuracy rate. Abraham et al. (2024) and Kumar et al. (2021) had lower accuracies of 92% and 88.12%, respectively. The trend indicates that the most precise diagnosis in neuro-oncology imaging is being achieved by the combination of deep learning and hybrid AI models.

Table 6: Summary of Key Studies on Histopathological Correlation and Biomarker Analysis in Metastatic Brain Tumors (2020–2025)

S. No.	Author(s), Year	Focus Area	Technique	Key Findings
1	**Proescholdt et al., 2025**	MRI-guided tissue sampling	Preoperative MRI + intraoperative microscopy	Identified prognostic significance of infiltrative histopathological growth patterns (HGPs) in metastatic lesions
2	**Madlener et al., 2025**	Non-invasive glioma monitoring	Liquid biopsy detecting	Achieved high sensitivity and

			ctDNA (H3F3A, BRAF V600E)	specificity for tumor mutation detection and monitoring
3	**Nocera et al., 2025**	Imaging-pathology correlation	MRI-based cellularity maps	Showed correlation between MRI-derived cellularity and tumor histopathological features
4	**Gao et al., 2024**	Tumor microenvironment	DTI-ALPS index + AQP4 expression	Linked glymphatic dysfunction to altered aquaporin-4 expression and tumor invasion potential
5	**Soto et al., 2024**	MRI volumetric analysis	Edema-to-tumor index (ETI)	Found limited histopathological correlation; ETI not predictive of biological aggressiveness
6	**Zhang et al., 2023**	Tumor subtype differentiation	Multiparametric MRI histogram + Ki-67 index	Differentiated lung cancer metastasis subtypes and predicted proliferation index non-invasively
7	**Widodo et al., 2023**	Tumor microenvironment analysis	ECM and immune cell profiling	Identified macrophages as dominant immunosuppressive cells in metastatic brain lesions
8	**Arzanforoosh et al., 2023**	Hypoxia and vascular mapping	MRI-derived OEF & VSM + histological HIF-1α, CD31	Revealed strong correlations between MRI metrics and hypoxia heterogeneity
9	**Kayahan et**	Imaging biomarkers	DWI/ADC	ADC values

	al., 2022		correlation with HER2 expression	correlated with tumor cellularity and HER2-positive metastases
10	**Dai et al., 2022**	Molecular bioinformatics	SOCS3 immune-oncogenic biomarker	Identified SOCS3 as regulator of tumor immune evasion and prognostic marker in gliomas
11	**Shi et al., 2022**	Radiogenomic modeling	Deep learning (ResNet) + EGFR/HER2 mutation status	Accurately predicted metastatic origin and molecular mutation from MRI subregions
12	**Yuksel et al., 2021**	Inflammatory biomarkers	C-reactive protein (CRP)	CRP distinguished metastases from gliomas and correlated with prognosis
13	**Scripcariu et al., 2022**	Immunohistochemistry in CRC metastases	HER2/neu nuclear staining	HER2/neu overexpression associated with poor survival outcomes
14	**Shaikh et al., 2020**	Radiomics and multi-omics biomarkers	Radiomics + ML integration	Highlighted AI-driven imaging biomarkers for tumor classification and prognosis
15	**Kondrup et al., 2020**	Serum biomarkers in NSCLC metastases	S100B	Showed limited predictive value as a serum marker for brain metastasis detection

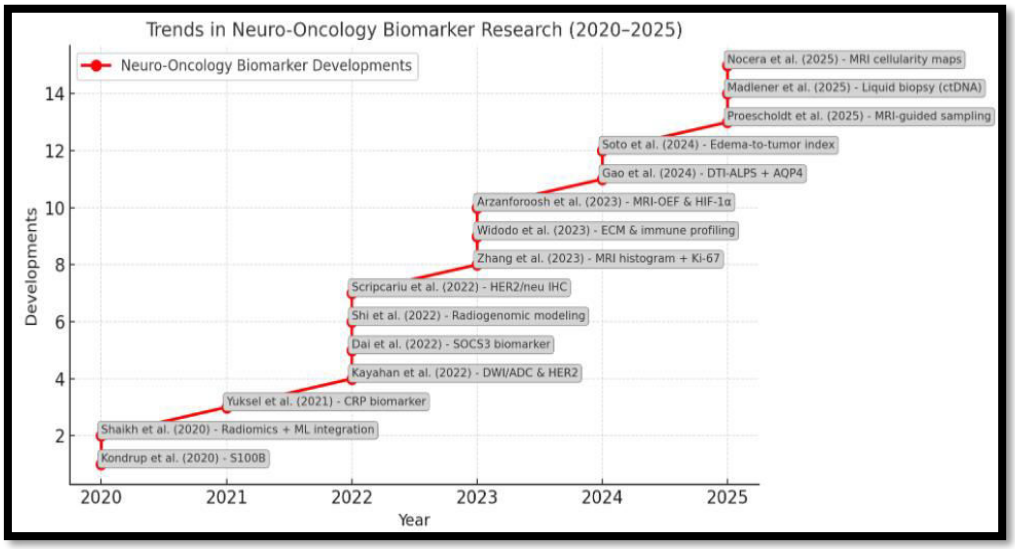


Figure 10: Neuro-Oncology Biomarker Research Trends (2020–2025)

Cumulative Developments in neuro-oncology biomarkers are depicted in Figure 10 against the Year. The rise of new biomarker developments started in 2020 with studies on S100B and Radiomics + ML integration. The figure shows a rapid increase in research, especially since 2022, with the total number of key developments climbing to 15 by 2025. Some major improvements consist of MRI methods (e.g., histogram, DWI/ADC, OEF, DTI-ALPS), liquid biopsy (ctDNA), and the discovery of new molecular markers such as HER2/neu, SOCS3, and HIF-1α. The latest 2025 records reflect pioneering efforts in MRI cellularity maps and MRI-guided sampling. The evidence indicates a solid and increasing confluence of sophisticated imaging and molecular technologies within the specialty.

4. Research Gap and Limitations

While MRI and CT have significantly progressed the early identification of metastatic brain tumors, there are still some deficiencies in terms of precision, understanding, and application in the clinic. Existing models have a hard time telling true progression from treatment effects, are devoid of standardized datasets, and mostly do not consider the integration of imaging with genomic or molecular data. The majority of AI-based methods focus on accuracy to the detriment of explainability, which hampers clinical trust and thus, a wider use. On the top of that, multimodal imaging is still expensive and not very comfortable with the idea of real-time or low-resource clinical use. The limitations are as follow:

- **Dataset Dependency:** Most studies rely on small or non-standardized MRI and CT datasets, which limits model generalization and introduces potential bias.
- **Computational Complexity:** Advanced AI and multimodal imaging models require high processing power, making real-time or low-resource deployment challenging.

- **Model Interpretability:** Deep learning models often act as "black boxes," reducing transparency and clinical trust in diagnostic decisions.
- **Limited Clinical Validation:** Many proposed approaches lack large-scale clinical trials, restricting their reliability and adoption in real-world healthcare settings

5. Conclusion

The present systematic review essentially supports the notion that the earliest recognition of metastasized brain tumors can be best achieved, when the modern imaging methods, computational intelligence, and histopathological examination are combined. The MRI and CT are still very much the primary diagnostic tools, at the same time, some newly developing methods like PET-MRI, MRS, and DTI can provide the more detailed view of tumor metabolism, vascularity, and microstructural changes. The usage of artificial intelligence and machine learning models—especially convolutional neural networks and hybrid algorithms—has been instrumental in achieving higher diagnostic accuracy by making lesion detection, segmentation, and classification more. One of the main points in these advancements is that they have not solved all the challenges, and some of them are limited diversity of the dataset, high computational power requirements, interpretability of the models, and the necessity for large-scale clinical validation. The correlation between histopathology and imaging still holds as the gold standard diagnostic tool, and it not only gives the molecular and cellular level pictures but also the insights into the imaging results and guidance of the selection of the suitable therapies through other methods. The combination of radiomics, radiogenomics, and biomarker analytics still holds the promise of creating a crossroad between the prediction based on imaging and biological confirmation, thus powering precision oncology. The focus of the future research should be on the creation of multimodal standardized frameworks, explainable AI models, and developing imaging technologies that will make diagnosing less of a guessing game, be more trustworthy in clinical settings, and allow for more personalized treatments. A combined effort of the radiology, pathology, and computation fields will play a key role in not only early detection but also in the improvement of survival rates of patients with metastatic brain tumors.

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