# Advances in Histopathological and Molecular Approaches to Brain Metastases: A Systematic Review

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**Abstract**

**Background:** Brain metastases are common secondary brain tumors that create major challenges for diagnosis and treatment. The differences in their appearance and molecular features make them difficult to classify. **Methods:** This review followed PRISMA 2020 guidelines. Research papers published between 2015 and 2025 were searched in Pub Med, Scopus, Web of Science, IEEE Xplore, and Science Direct. Only English-language studies focused on histopathology, immunohistochemistry, molecular testing, and AI-based digital pathology were included. **Results:** A total of 687 studies were found, and 54 met the inclusion criteria. Traditional stains such as hematoxylin and eosin (H&E) and markers like TTF-1, CK7, CK20, GFAP, and GATA3 are still useful for identifying the origin of tumors. Newer techniques like multiplex immunohistochemistry and molecular testing provide more detailed information about tumor genetics. Artificial intelligence applied to whole-slide images improves accuracy and consistency in diagnosis. However, most AI studies are limited by small datasets and lack standardization across laboratories. **Conclusions:** Combining molecular testing with AI-based digital pathology can help doctors diagnose brain metastases more accurately and predict patient outcomes better. Future studies should include larger datasets, use explainable AI systems, and follow standardized laboratory methods.

**Keywords:** brain metastases, histopathology, immunohistochemistry, multiplex IHC, digital pathology, artificial intelligence, biomarkers, systematic review

## 1 Introduction

Brain metastases are the most common secondary brain tumors in adults and are seen in nearly 40% of cancer patients during the course of their illness [1,2]. The primary sources are usually cancers of the lung, breast, skin (melanoma), kidneys, and digestive system [3,4]. The higher occurrence of brain metastases in recent years is partly due to better systemic therapies that extend patient survival, giving cancer more time to spread to the central nervous system (CNS) [5]. Even with progress in imaging and treatment, tissue-based diagnosis continues to play a crucial role in confirming metastasis and deciding therapy [6,7]. Conventional histopathology using hematoxylin and eosin (H&E) staining remains a key diagnostic tool, but it often cannot clearly identify the primary tumor site [8]. Immunohistochemistry (IHC) therefore serves as a valuable method to detect lineage and tissue-specific markers, such as thyroid transcription factor-1 (TTF-1), cytokeratins (CK7 and CK20), glial fibrillary acidic protein (GFAP), and GATA3 [9–12]. These markers assist in differentiating metastatic lesions from primary brain tumors and are especially important in cases where the primary cancer site is unknown [13].

The field has advanced with the introduction of multiplex immunohistochemistry (mIHC) and multiplex immunofluorescence (mIF) which make it possible to observe several biomarkers on one tissue sample. This allows researchers to study spatial relationships and molecular variations within tumors [14,15]. Similarly, molecular pathology methods—such as next-generation sequencing (NGS), fluorescence in situ hybridization (FISH) and RNA-based assays—provide deeper information about tumor genetics and help detect clinically significant mutations [16–18]. Digital pathology combined with artificial intelligence (AI) is now transforming histopathology. Deep learning models trained on whole-slide images (WSIs) can identify tumor areas, classify subtypes, and even predict genetic changes with improved precision [19–22]. These techniques enhance diagnostic accuracy, minimize observer bias, and allow for large-scale analysis across institutions [23,24].

However, the lack of standardization in sample preparation, variation in biomarker expression, and limited generalizability of AI algorithms remain significant barriers to clinical application [25–28]. There is also a growing need to validate new diagnostic methods and to integrate molecular, digital, and morphological data for more reliable clinical use [29, 30].

**Objective:** This review summarizes recent progress in histopathological, molecular and AI-based methods used to study brain metastases. It also identifies current research gaps and suggests areas for improvement.

## 2 Review Methodology

To ensure clarity and scientific accuracy throughout the review process, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed [31].

### 2.1 Search Strategy

A detailed search was performed to collect studies related to the histopathological analysis of brain metastases. The databases PubMed, Scopus, Web of Science, IEEE Xplore, and Science Direct were used to find relevant peer-reviewed research papers published between 2015 and 2025.

The search terms were developed using keywords and controlled vocabulary. Four main areas were covered:

- Histopathology – terms such as "H&E staining," "histological analysis," and "morphology."
- Brain Metastases – terms like "brain metastases," "intracranial secondary tumors," and "CNS metastasis."
- Immunohistochemistry (IHC) – including "TTF-1," "CK7," "CK20," "GFAP," and "multiplex IHC."
- Artificial Intelligence and Digital Pathology – including "deep learning," "whole-slide imaging," "CNN," and "AI in pathology."

These terms were combined using Boolean operators (AND/OR) to increase search accuracy [31–33]. Only full-text English-language articles were included. Conference abstracts, editorials, and theses were excluded to keep the focus on original research. The search strategy and keywords were checked against earlier systematic reviews to ensure completeness [34,16]. A total of 687 articles were identified through this initial screening process. Table 1 outlines the search strategy and keyword combinations.

| Database | Years Covered | Search Terms / Keywords | Boolean Used |
|---|---|---|---|
| Pub Med | 2015–2025 | "brain metastases", "histopathology", "IHC", "CNN", "digital pathology" | AND, OR |
| Scopus | 2015–2025 | "multiplex IHC", "deep learning", "whole-slide imaging" | AND, OR |
| Web of Science | 2015–2025 | "metastatic brain tumor", "AI-based pathology" | AND, OR |
| IEEE Xplore | 2015–2025 | "CNN", "U-Net", "transformer models", "digital pathology" | AND, OR |

**Table 1: Search strategy and keywords used in the systematic review**

| Author (Year) | Dataset | AI Model / Method | Metric | Key Outcome |
|---|---|---|---|---|
| Campanella et al. (2019) | Whole-slide images | Weakly supervised CNN | AUC 0.94 | Improved classification accuracy |
| Coudray et al. (2018) | TCGA dataset | Res Net-based CNN | Accuracy 85% | Mutation prediction (EGFR, KRAS) |
| Wang et al. (2022) | Histology from lung cancer | AI classifier | AUC 0.91 | Predicted brain metastasis risk |
| Lu et al. (2020) | Metastasis dataset | CNN | Sensitivity 92% | Automated metastasis detection |
| Nicholson et al. (2018) | Institutional dataset | Standard histology | — | Optimized pathology protocol |

**Table 2: Summary of Included Studies**

Table 2 summarizes representative studies that applied artificial intelligence and digital pathology models to histopathological datasets, including work by Campanella et al. [22], Coudray et al. [20], Wang et al. [24], Lu et al. [23].

### 2.2 Inclusion and Exclusion Criteria

Studies were included if they met the following conditions:

- Focused on histopathological, immunohistochemical, or AI-based analysis of brain metastases [9–24].
- Used multiplex staining, digital pathology, or computational imaging approaches.
- Reported measurable diagnostic or prognostic results with statistical evidence.

**The following were excluded:**

- Non-English papers.
- Studies without quantitative histological data.
- Reviews, case reports, letters or editorials.
- Research that focused only on primary brain tumors rather than metastases.

### 2.3 Study Selection Process

Three primary stages comprised the selection process: identification, screening, and ultimate inclusion (shown in Figure 1). Following the initial removal of duplicates, 534

papers remained for screening. 480 of these were eliminated after the abstracts and titles were examined. 54 articles were ultimately chosen for in-depth qualitative examination.

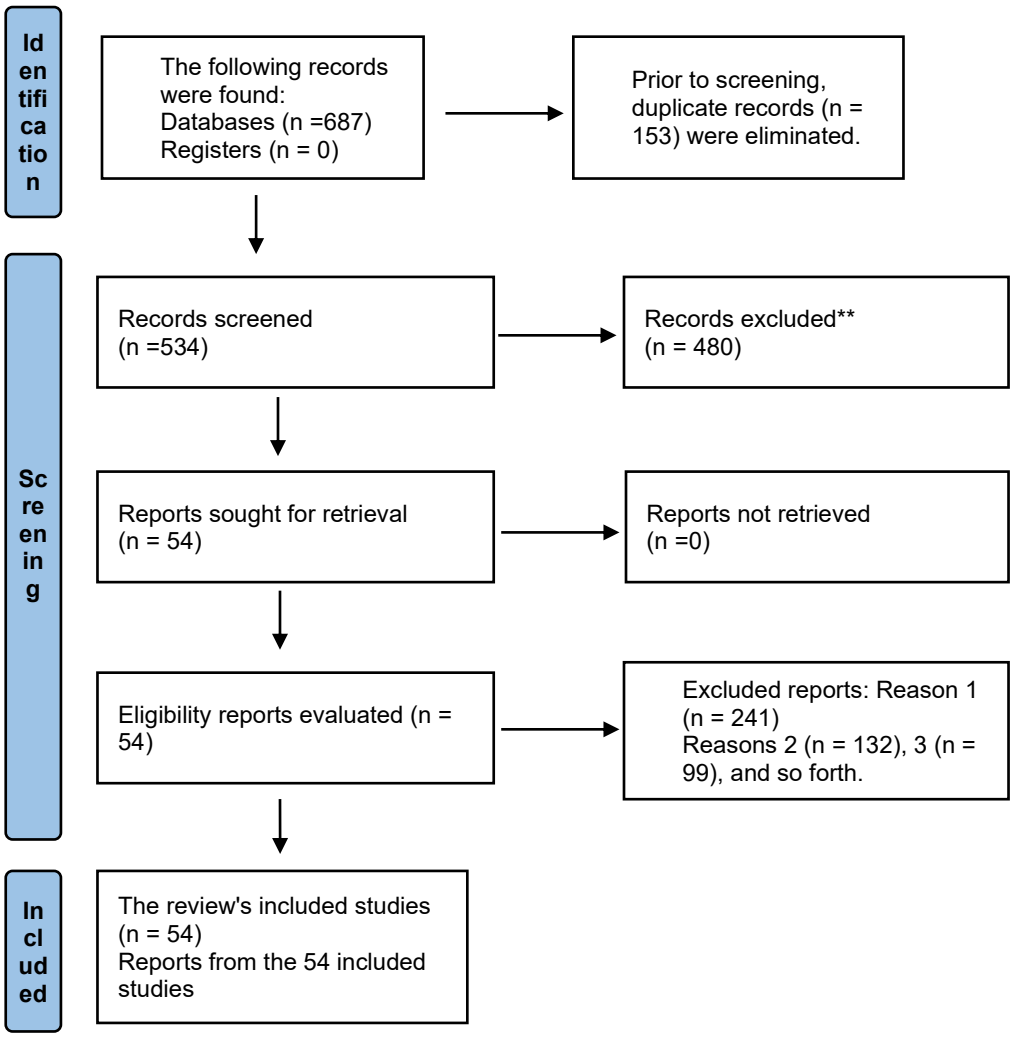


**Figure 1 PRISMA flowchart**

**Main reasons for exclusion were:**

- Insufficient histopathological data (241 studies).
- Lack of relevance to brain metastasis (132 studies).
- Weak methodology or unclear results (99 studies).
- Unavailable full text (19 studies).

### 2.4 Quality Assessment and Data Extraction

To ensure scientific quality, each selected paper was reviewed using the Critical Appraisal Skills Programme (CASP) checklist for diagnostic studies and reporting standards such as TRIPOD and CLAIM [32,33].

**The following information was extracted from each study:**

- Type of study and number of samples.
- Biomarkers used (e.g., TTF-1, CK7, CK20, GFAP, GATA3).
- Imaging methods (e.g., WSI, mIHC, mIF).
- AI models or computational approaches (CNN, U-Net, transfer learning, ensemble methods).
- Diagnostic metrics such as sensitivity, specificity, and AUC values.

Data extraction was done separately by two reviewers. Discussions with a third reviewer helped to settle disagreements. Cohen's kappa coefficient was used to measure reviewer consistency (K = 0.87), indicating strong agreement [34].

### 2.5 Data Synthesis

The results of the selected studies were grouped and analyzed through narrative synthesis rather than statistical pooling, due to variation in data types and metrics. The studies were classified based on four themes:

- Traditional histological methods.
- Immunohistochemical markers.
- Advances in digital pathology.
- AI-based image processing and prediction models.

No meta-analysis was performed because of differences in imaging platforms, staining methods, and reporting standards.

## 3 Literature Analysis

The study of brain metastases through histopathology has developed quickly in recent years. Researchers have focused on improving traditional staining methods, discovering new biomarkers, and applying digital and artificial intelligence (AI) tools to analyze tissue samples. The goal of these advances is to improve diagnostic accuracy, reduce observer bias, and identify the primary origin of metastatic tumors. This section reviews the major developments in histopathological, molecular, and AI-based techniques that support better understanding and diagnosis of brain metastases.

### 3.1 Traditional Histopathological and IHC Techniques

Conventional staining methods such as hematoxylin and eosin (H&E) remain the first step in examining brain metastases [9, 12]. These stains allow visualization of tumor structure and cellular details. However, morphology alone often cannot confirm the origin of the tumor. Therefore, immunohistochemistry (IHC) plays an essential role in diagnosis. It uses antibodies to detect proteins that indicate the tissue or organ of origin.
Recent studies demonstrate that AI-based histopathology can predict the development of brain metastases from lung cancer [19] and meta-analyses have confirmed the diagnostic

accuracy of digital pathology models across multiple tumor types [20]. Moreover, common immunohistochemical markers such as thyroid transcription factor-1 (TTF-1), cytokeratins (CK7 and CK20), glial fibrillary acidic protein (GFAP), and GATA3 are essential for distinguishing primary brain tumors from secondary (metastatic) lesions [11–13]. For instance, Miettinen et al. [11] showed that TTF-1 and CK7/CK20 patterns can help distinguish lung and colorectal metastases. Deep learning algorithms have shown superior performance in detecting micro-metastases and predicting patient outcomes from histopathological images [19-20].Integration of molecular profiling with AI-based image analysis enables more accurate classification and prognosis of brain metastases [18].

Recent studies have expanded traditional IHC by introducing multiplex immunohistochemistry (mIHC) and multiplex immunofluorescence (mIF). These methods can detect several markers on the same tissue section, preserving spatial and structural information. They help pathologists study how tumor cells interact with their microenvironment and immune cells [14,15]. Overall, IHC and multiplex staining remain reliable methods for diagnosing and characterizing brain metastases.

### 3.2 Molecular and Digital Pathology Techniques

Molecular testing and digital imaging have become key additions to classical pathology. Techniques such as next-generation sequencing (NGS), RNA sequencing, and fluorescence in situ hybridization (FISH) have identified important genetic mutations in metastatic tumors [16, 17]. Recent studies have shown that deep learning–based histopathological analysis can significantly improve both diagnostic accuracy and prognostic prediction in brain metastases [18].

Digital pathology allows histology slides to be scanned and analyzed on a computer. Whole-slide imaging (WSI) enables large-scale storage and study of tissue architecture. Using AI and machine learning models, digital pathology can detect and classify tumor regions automatically. For example, Campanella et al. [22] and Cruz-Roa et al. [19] used convolutional neural networks (CNNs) to accurately identify metastases in histology slides. These methods reduce diagnostic time and improve consistency among pathologists [20]. Wang et al. [24] demonstrated that AI models can predict the likelihood of brain metastases from lung cancer samples, showing the predictive value of image-based analysis. Overall, digital pathology has transformed how tissues are examined by combining speed, accuracy and scalability with molecular data.

### 3.3 AI-Driven Models and Hybrid Approaches

Artificial intelligence has become a powerful tool in pathology. Models based on deep learning, such as U-Net, Res Net, and transformer-based networks, can automatically segment tumors, identify microstructures, and even predict mutations [20,22]. Coudray et

al. [22,23] applied CNNs to classify lung adenocarcinomas and predict EGFR and KRAS mutations directly from H&E-stained images. These studies demonstrate that AI can provide both diagnostic and molecular insights from a single image source. Recent progress in explainable artificial intelligence (XAI) has improved the interpretability of AI-assisted histopathological models, helping pathologists understand model predictions [26].

Integration of artificial intelligence and digital pathology continues to enhance tumor characterization and improve diagnostic precision in metastatic brain lesions [24].Standardization in digital pathology has been identified as a key step toward ensuring reproducibility and interoperability across laboratories [27,28].

## 4. Research Gaps and Limitations

Despite major progress in histopathological and AI-based analysis of brain metastases, several gaps and limitations still exist that affect clinical use and scientific consistency. Addressing these gaps will be essential to improve diagnostic precision and develop more reliable, standardized systems for patient care.

### 4.1 Research Gaps

#### Limited Multicenter Datasets

Many artificial intelligence and digital pathology studies are based on small datasets collected from single institutions. This limits how well these models can perform on data from other hospitals or populations. Larger, multicenter datasets are needed to improve the generalization and reliability of AI models across different regions, scanners, and patient groups.

#### Weak Integration Between Molecular and AI Data

Although AI models are effective in analyzing digital slides, few studies combine this information with molecular data such as genetic mutations or RNA profiles. Integrating these two types of data could create stronger diagnostic and prognostic models that better reflect tumor biology.

#### Lack of Standardization in Image Processing

There are major differences in how researchers prepare and process images. Color normalization, slide scanning, and artifact removal techniques vary widely, making it hard to compare results across studies. The absence of standard image-preprocessing guidelines reduces reproducibility and affects model accuracy.

#### Limited Use of Explainable AI

Most AI models work as “black boxes,” meaning they provide results without explaining how the decision was made. There is little research using explainable AI (XAI) tools that

can show which features influenced a diagnosis. Improving interpretability is important for clinical acceptance and regulatory approval.

**Underuse of Multiplex Staining in Routine Practice**

Although multiplex immunohistochemistry (mIHC) and multiplex immunofluorescence (mIF) offer detailed insights into tumor biology, they are not widely used in clinical laboratories. The reasons include high cost, long processing time, and lack of technical expertise. Simplifying these methods could help them become part of everyday diagnostic work.

### 4.2 Limitations of the Review

- This review also has several limitations that should be acknowledged:
- Language Restriction: Only English-language studies were included. Research published in other languages may contain useful information that was not reviewed.
- Exclusion of Unpublished Work: Preprints, theses, and conference proceedings were excluded to maintain quality, but this might have left out new and emerging findings.
- Heterogeneous Evaluation Metrics: The selected studies used different statistical measures such as AUC, sensitivity, and F1 score, which made direct comparison difficult.
- Computational Bias: Many AI-based studies focused mainly on accuracy and ignored aspects such as interpretability, robustness, or clinical utility.
- Narrow Scope: This review mainly focused on tissue-based histopathology. Other diagnostic tools such as radiomics or liquid biopsy were not discussed, even though they may complement histological findings.

## 5. Conclusions

Histopathology remains central to diagnosing brain metastases, but it is becoming more powerful when combined with molecular testing and AI-assisted digital pathology. Together, these methods improve diagnostic precision and allow better understanding of tumor biology. For clinical application future studies should develop larger, multi-center datasets, adopt explainable AI models, and follow standardized laboratory procedures.

## List of Abbreviations

AI – Artificial Intelligence
AUC – Area under the Curve
CASP – Critical Appraisal Skills Programme
CK7 – Cytokeratin 7
CK20 – Cytokeratin 20
CLAIM – Checklist for Artificial Intelligence in Medical Imaging
DL – Deep Learning
EGFR – Epidermal Growth Factor Receptor

GFAP – Glial Fibrillary Acidic Protein
H&E – Hematoxylin and Eosin
IHC – Immunohistochemistry
mIHC – Multiplex Immunohistochemistry
mIF – Multiplex Immunofluorescence
NGS – Next-Generation Sequencing
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Res Net – Residual Neural Network
TTF-1 – Thyroid Transcription Factor-1
TRIPOD – Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
U-Net – Convolutional Neural Network Architecture for Image Segmentation
WSI – Whole-Slide Imaging
XAI – Explainable Artificial Intelligence

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