Journal of Computing and Electronic Information Management
ISSN: 2413-1660 | Vol. 20, No. 3, 2026

A Review of Deep Learning Methods for Brain Tumor Segmentation with Missing Modalities

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Abstract: Multi-modality imaging significantly enhances the accuracy and reliability of brain tumor segmentation by providing complementary biological information. However, in clinical practice, obtaining a complete set of Magnetic Resonance Imaging (MRI) modalities is often hindered by equipment, time, and cost constraints. The challenge of missing modalities thus becomes a major obstacle to achieving high-performance segmentation. This paper systematically reviews emerging methods addressing this issue, with a focus on their network architectures. The main strategies include data synthesis for generating missing scans, hetero-modal segmentation utilizing flexible architectures for variable inputs, and Knowledge Distillation (KD), which transfers knowledge from models trained on complete datasets. Building on these foundations, we analyze the novelty, strengths, and limitations of each method. To provide context, we also introduce commonly used MRI datasets. Ultimately, this review aims to deliver a comprehensive performance evaluation of compensation techniques and outline promising future directions for overcoming this persistent clinical challenge.

Keywords: Missing modality; Brain tumor segmentation; Magnetic Resonance Imaging (MRI).

1. Introduction

In neuro-oncology, Magnetic Resonance Imaging (MRI) [1-2] is recognized as the gold standard for non-invasive diagnosis, monitoring, and treatment planning of brain tumors. Its strength lies not in a single imaging protocol, but in the synergistic use of multiple sequences (modalities), each offering a unique and complementary perspective on the complex pathophysiology of neoplastic tissues. The standard clinical and research protocol, exemplified by the widely used Brain Tumor Segmentation (BraTS) [3] benchmark dataset, includes four key MRI sequences: T1-weighted (T1w), T1-weighted contrast-enhanced (T1ce), T2-weighted (T2w), and T2 Fluid-Attenuated Inversion Recovery (FLAIR). Integrating information from these modalities is essential for the comprehensive characterization of gliomas, the most common primary brain tumors.

Each modality provides distinct tissue contrast, highlighting specific components of the tumor and surrounding brain structures. As illustrated in Figure 1, T1w imaging offers excellent anatomical detail, clearly delineating gray and white matter, but often presents the tumor as a hypointense, poorly defined mass. The use of a gadolinium-based contrast agent in T1ce imaging is transformative, enhancing areas where the blood-brain barrier is compromised by tumor activity and making the active, enhancing tumor (ET) appear hyperintense. This sequence is critical for identifying the most aggressive tumor regions. T2w imaging is highly sensitive to changes in tissue water content, depicting areas of vasogenic edema—swelling in the brain tissue surrounding the tumor—as hyperintense regions. The FLAIR sequence, a specialized T2-weighted technique, suppresses the signal from cerebrospinal fluid (CSF), preventing CSF-filled spaces like the ventricles from obscuring peritumoral edema, which also appears hyperintense on FLAIR images. The true diagnostic power of multi-modal MRI emerges from the fusion of this reciprocal information.

Despite the immense clinical value of multi-modal MRI, its practical application is frequently hindered by the missing modality problem. In real-world clinical settings, acquiring a complete set of T1w, T1ce, T2w, and FLAIR sequences is often challenging due to varying scanning protocols, limited machine availability, or patient-specific constraints. To bridge this gap, significant research efforts have been dedicated to developing robust segmentation frameworks that can operate effectively with incomplete data.

This paper provides a systematic review of emerging methods addressing this issue, categorizing them into three primary technical trajectories based on their network architectures and learning paradigms:

Data Synthesis: These methods focus on "filling the gap" by generating high-fidelity missing scans from available modalities, typically leveraging Generative Adversarial Networks (GANs) or Diffusion Models to restore the complete input space.

Hetero-modal Segmentation: Instead of data recovery, these approaches utilize flexible architectures—such as shared encoders or modality-specific fusion layers—to adaptively process any combination of variable inputs during inference.

Knowledge Distillation (KD): This strategy involves transferring sophisticated spatial and semantic features from a "teacher" model (trained on complete datasets) to a "student" model, thereby enhancing the segmentation performance of the latter when dealing with limited modalities.

By critically evaluating the strengths and limitations of these strategies, this review provides a systematic taxonomy and a comprehensive roadmap, offering researchers a clear perspective on the current landscape and future directions for addressing modality incompleteness in medical image segmentation.

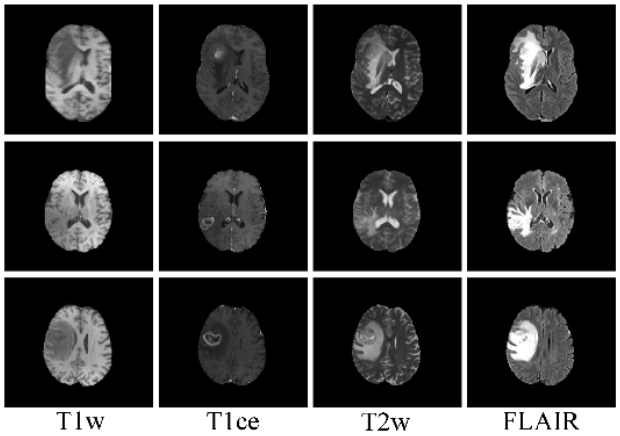

Figure 1. Visualization of brain tumor segmentation across multiple MRI modalities. From left to right: MRI images in four modalities (T1w, T1ce, T2w, and FLAIR) are shown for three different patients.

2. Methodologies for Handling Missing Modalities

The missing-modality problem has been consistently identified as a key bottleneck for robust brain tumor segmentation in both benchmark and clinical settings [4-5]. A central observation across studies is that models trained on full modalities often exhibit precipitous performance degradation when one or more critical sequences are unavailable, particularly T1ce for enhancing tumor delineation and FLAIR for edema-sensitive regions. Existing solutions can be grouped into three paradigms: knowledge distillation (KD) [6-8], hetero-modal learning [9] and data synthesis [10-12]. These paradigms differ not only in architectural design but also in their assumptions about supervision, inference cost, and failure modes.

At a high level, KD methods leverage privileged multi-modal knowledge from a teacher network to a student network designed for incomplete inputs. Hetero-modal learning approaches aim to develop a unified model that is inherently robust to any permutation of available modality subsets. Data synthesis methods focus on reconstructing missing modalities before or jointly with segmentation. The following sections provide a comprehensive exposition of these three paradigms.

2.1. Knowledge Distillation (KD)

KD[8,13-15] has become one of the most effective supervised strategies for missing-modality segmentation because it decouples training-time information richness from inference-time input availability. Following the teacher-student formulation introduced by Hinton et al[16], medical segmentation studies train a teacher on complete modalities and force a student to approximate the teacher while receiving incomplete inputs. This setup is particularly attractive when deployment requires lightweight models or low-latency inference, since much of the multimodal prior is transferred during training rather than reconstructed at test time.

Output-level KD remains the most widely adopted variant [17-18]. In this formulation, softened teacher logits expose inter-class structure and uncertainty cues that are absent in hard labels, which is especially valuable for ambiguous boundaries in edema and tumor core regions [19-20]. Empirically, output distillation is easy to integrate and stable to optimize, but its supervision granularity is limited because it constrains only final predictions, not internal representation geometry.

A stronger direction is feature-level KD, where intermediate representations are aligned between teacher and student. Compared with pure logit matching, feature distillation typically provides denser supervisory signals and can better preserve morphology-aware latent structure when modalities are missing. However, its benefit depends on where alignment is imposed; overly rigid layer-wise matching may reduce student flexibility, especially when modality-conditioned feature statistics differ substantially.

Recent KD extensions include prototype-aware distillation, teacher-assistant-student collaboration, and generalized unimodal transfer from multimodal experts. These variants address limitations of vanilla KD by improving class-level consistency, training stability, and transferability to severe modality-reduction scenarios. Overall, KD offers a favorable accuracy-efficiency profile, but its ceiling is constrained by teacher quality and by train-test distribution gaps in missing-modality patterns.

2.2. Hetero-modal Methods

Hetero-modal methods are motivated by the combinatorial explosion of modality subsets and aim to train a single model that remains functional under arbitrary input combinations [21]. The foundational HeMIS framework demonstrated that modality-specific encoding plus shared statistical fusion can maintain competitive segmentation without requiring separate models for each missing case. Subsequent studies extended this idea to broader clinical settings and dataset shifts, confirming that unified hetero-modal training is practical for real-world deployment [22].

A key architectural axis is shared versus modality-specific encoding. Shared-encoder designs are parameter-efficient and simple to train [23-25], but they may under-represent modality-specific low-level cues and are more sensitive to naive input imputation strategies (e.g., zero filling) [26-27]. In contrast, separate encoders can preserve modality-specialized features and often improve robustness under severe missingness, at the cost of higher model complexity [28-29].

Fusion design is the dominant factor governing hetero-modal performance. Earlier fusion schemes relied on concatenation or summation, while newer methods use attention and gating to dynamically modulate each modality contribution [30-32]. These mechanisms are clinically meaningful: T1ce-related channels are often emphasized for active tumor boundaries, whereas FLAIR-sensitive channels are amplified for edema regions. More recent transformer-based models explicitly capture long-range cross-modal dependencies and have shown improved consistency in incomplete-input settings [33-36].

Despite strong robustness and fast one-stage inference, hetero-modal methods still face two challenges. First, training quality depends on how well missing patterns in training match deployment reality; unrealistic masking policies can reduce generalization [37]. Second, as architectures become more expressive (e.g., multi-branch transformers), computational cost may increase, narrowing their practical advantage over simpler KD students in resource-constrained scenarios.

2.3. Data Synthesis

Data synthesis methods explicitly reconstruct missing

modalities and then perform segmentation, either in a two-stage pipeline or in jointly optimized architectures [10-12]. The main advantage is compatibility with standard full-modality segmentation networks, which allows reuse of mature backbones once synthetic channels are generated. This paradigm is especially attractive when downstream segmentation models are fixed in clinical workflows.

Early synthesis approaches based on AEs/VAEs learn cross-modal mappings through latent compression and reconstruction [38-39]. These methods are stable and conceptually simple, but their pixel-wise objectives (MSE/L1) often favor averaged solutions, producing over-smoothed outputs with limited high-frequency detail, which can weaken boundary-sensitive segmentation performance.

GAN-based synthesis addresses this limitation by adding adversarial supervision to improve realism [40]. Recent works further combine synthesis and segmentation with consistency constraints or hyper-network designs to reduce train-test mismatch between generated and real modalities. Such joint designs often improve task relevance compared with standalone image translation, because the generator is guided by segmentation-oriented objectives rather than appearance quality alone.

Nevertheless, synthesis methods remain sensitive to domain shift and error propagation. If generated modalities contain structural artifacts or hallucinated intensity patterns, segmentation errors can be amplified in downstream stages [40]. They also tend to incur higher inference overhead in two-stage settings. Therefore, while synthesis can be effective under severe missingness, it is most reliable when combined with uncertainty-aware quality control and task-coupled optimization [41].

In summary, the three paradigms exhibit complementary strengths: KD emphasizes efficient knowledge transfer, hetero-modal methods prioritize direct robustness to variable inputs, and synthesis methods attempt explicit information recovery. In practice, the most suitable paradigm depends on missing-pattern uncertainty, computational budget, and deployment constraints.

3. Datasets and Performance Review

The BraTS (Multimodal Brain Tumor Segmentation) challenge, held annually in conjunction with the prestigious Medical Image Computing and Computer Assisted Intervention (MICCAI) conference, has been instrumental in driving progress in this field. Each year, the organizers release a large and meticulously curated dataset, which has grown in size and diversity over the years, as shown in Table 1.

Table 1. BraTS dataset utilized in the literature work to evaluate the performance of missing modality compensate networks.

Dataset	Num Samples	Modalities
BraTS 2013	30 subjects: 20 High-Grade Gliomas (HGG) and 10 Low-Grade Gliomas (LGG)	T1, T1c, T2, FLAIR
BraTS 2015	274 subjects: 220 High-Grade Gliomas (HGG) and 54 Low-Grade Gliomas (LGG)	T1, T1c, T2, FLAIR
BraTS 2017	285 subjects: 210 High-Grade Gliomas (HGG) and 75 Low-Grade Gliomas (LGG)	T1, T1c, T2, FLAIR
BraTS 2018	285 subjects: 210 High-Grade Gliomas (HGG) and 75 Low-Grade Gliomas (LGG)	T1, T1c, T2, FLAIR
BraTS 2019	335 subjects: 259 High-Grade Gliomas (HGG) and 76 Low-Grade Gliomas (LGG)	T1, T1c, T2, FLAIR
BraTS 2020	369 subjects: Primarily Gliomas	T1, T1ce, T2, FLAIR
BraTS 2021	2040 subjects: Primarily Gliomas	T1, T1ce, T2, FLAIR
BraTS 2022	1251 subjects (training set): Primarily Gliomas	T1, T1ce, T2, FLAIR
BraTS 2023	1251 subjects (training set): Primarily Gliomas	T1, T1ce, T2, FLAIR

3.1. Data Characteristics

Modalities: The BraTS dataset provides four core MRI modalities for each patient case. All images are pre-processed, including co-registration to a standard anatomical template, resampling to a uniform isotropic resolution (1x1x1 mm^3), and skull-stripping. This significantly lowers the barrier to entry for researchers. The four modalities are:

T1w: Provides clear anatomical contrast of brain tissues.

T1ce: A T1 scan after injection of a contrast agent, which highlights the active, blood-rich parts of the tumor.

T2w: Highly sensitive to vasogenic edema, making it useful for identifying swelling around the tumor.

Fluid-Attenuated Inversion Recovery (FLAIR): Similar to T2 but with the cerebrospinal fluid (CSF) signal suppressed, making it excellent for visualizing peritumoral edema.

Pathology and Scale: The dataset consists of pre-operative MRI scans from patients with brain gliomas, including both high-grade gliomas (HGG) and low-grade gliomas (LGG). The data is collected from multiple institutions, ensuring a degree of variability. Recent editions of the challenge provide hundreds of cases for training and a smaller set for validation, with a separate, hidden testing set used for official evaluation on an online platform.

3.2. Annotation Details

The ground-truth segmentation masks are manually annotated by expert neuroradiologists and are provided only for the training dataset. The annotations are divided into several primary labels that correspond to distinct tumor sub-regions:

Necrotic and Non-Enhancing Tumor Core (NCR/NETC): The non-viable or non-enhancing central part of the tumor.

Peritumoral Edema (ED): The swelling in the brain tissue surrounding the tumor.

Gadolinium-Enhancing Tumor (ET): The active part of the tumor, which is highlighted by the contrast agent.

For evaluation, these primary labels are combined into three clinically relevant, nested composite regions, which form the basis of the challenges scoring metrics:

Whole Tumor (WT): Encompasses all three sub-regions (NCR/NETC + ED + ET).

Tumor Core (TC): Includes the active and necrotic parts of the tumor (NCR/NETC + ET).

Enhanced Tumor (ET): Consists only of the active tumor core.

3.3. Performance Review

This section provides a comprehensive review of the performance of various methods designed to address the missing modality challenge in brain tumor segmentation. We first introduce the primary metrics used for evaluation and then present a quantitative analysis comparing the efficacy of the different paradigms discussed in this paper.

To objectively measure and compare the accuracy of segmentation algorithms, several standardized metrics are employed. Among these, the Dice Similarity Coefficient (DSC) is the most widely used and important metric in the field of medical image segmentation, and it serves as the primary metric in the BraTS challenge.

The DSC is an overlap-based metric that measures the spatial similarity between the predicted segmentation map (P) and the ground-truth annotation (G). It is defined as twice the area of the intersection of the two sets, divided by the sum of their areas. A higher DSC value indicates a better match between the prediction and the ground truth.

The formula is given by:

$$\mathrm{DSC}(P,G) = \frac{2\times|P\cap G|}{|P|+|G|} \qquad (1)$$

The DSC score ranges from 0 to 1, where 0 indicates no overlap and 1 indicates a perfect match. In the context of the BraTS challenge, DSC is calculated separately for the three clinically relevant, nested regions: WT, TC, and ET. This allows for a nuanced evaluation of an algorithms ability to segment different tumor sub-structures.

Quantitative comparison results measured in DSC (%) on BraTS2020 are shown in Table 2.

Table 2. Quantitative comparison results measured in DSC (%) on BraTS2020

Type	FLAIR	○	○	○	●	○	○	●	○	●	●	●	●	●	○	●	Average
	T1w	○	○	●	○	○	●	●	●	○	○	●	●	○	●	●	
	T1ce	○	●	○	○	●	●	○	○	○	●	●	○	●	●	●	
	T2w	●	○	○	○	●	○	○	●	●	○	○	●	●	●	●	
WT	PPIL[39]	87.6	80.4	81.1	88.6	88.2	82.7	89.6	88.1	90.4	90.0	90.3	90.6	90.8	88.4	91.0	87.9
	RFNet[42]	86.0	76.7	77.1	87.3	87.7	81.1	89.7	87.7	89.8	89.8	90.6	90.6	90.6	88.3	91.1	86.9
	RobustSeg[43]	82.2	71.3	71.4	82.8	85.9	76.8	88.1	85.5	88.0	87.3	88.8	89.2	88.6	86.6	89.4	84.1
	MFI[37]	85.3	73.1	69.4	85.1	88.0	77.4	89.2	86.9	89.5	89.2	90.0	90.2	90.5	87.8	90.8	85.5
	M2FTrans[36]	87.2	78.8	79.1	88.7	88.6	82.4	90.3	88.3	90.5	90.3	91.0	90.9	91.1	89.0	91.3	87.8
TC	PPIL[39]	73.1	84.4	68.2	72.0	86.1	84.8	72.8	74.2	75.4	85.7	85.7	75.6	86.3	86.0	86.3	79.8
	RFNet[42]	71.0	81.5	66.0	69.1	83.4	83.4	73.0	73.1	74.1	84.6	85.0	75.1	84.9	83.5	85.2	78.2
	RobustSeg[43]	61.8	76.6	54.3	60.7	82.4	80.2	68.1	66.4	68.2	81.8	82.7	70.4	81.8	82.8	82.8	73.4
	MFI[37]	66.6	78.5	54.7	65.0	84.3	81.6	71.5	69.5	71.2	83.9	85.2	72.5	84.8	84.8	85.5	76.0
	M2FTrans[36]	72.3	81.8	66.7	72.2	84.6	83.7	74.4	73.6	75.4	85.5	85.8	76.1	85.2	84.9	85.4	79.2
ET	PPIL[39]	50.3	81.8	40.3	44.6	81.1	81.8	44.4	49.7	53.1	82.1	82.1	52.4	81.2	81.1	81.3	65.8
	RFNet[42]	46.2	74.8	37.3	38.1	75.9	78.0	40.9	45.6	49.3	76.6	76.8	49.9	77.1	77.0	78.0	61.4
	RobustSeg[43]	36.4	67.9	28.9	34.6	71.4	70.1	39.6	39.9	42.1	70.7	71.7	43.9	71.1	71.8	71.5	55.4
	MFI[37]	43.5	74.0	29.6	39.4	80.1	78.3	42.8	47.1	46.7	80.1	81.4	47.0	80.4	80.4	81.9	62.2
	M2FTrans[36]	51.5	82.5	40.8	43.3	82.3	83.8	47.0	49.9	53.8	83.0	84.1	53.3	81.2	82.3	82.1	66.7

4. Summary

This paper presents a comprehensive review of methodologies for addressing missing MRI modalities in brain tumor segmentation. We systematically categorize the literature into two primary paradigms: supervised approaches, including Knowledge Distillation (KD) and Hetero-modal methods, which adapt to incomplete data; and unsupervised approaches, such as non-adversarial Data Synthesis and Generative Adversarial Networks (GANs), which aim to reconstruct missing data. For each strategy, we analyze its core principles, network architecture, and performance trade-offs, supported by discussion of the standard BraTS benchmark, the primary DSC evaluation metric, and quantitative performance summaries. By providing a structured overview from foundational concepts to state-of-the-art techniques, this work serves as a detailed reference for researchers, clearly mapping the current landscape of solutions for this persistent clinical challenge.

Future research should focus on several key directions. First, unified and scalable missing-modality frameworks are needed so that a single model can remain robust across arbitrary modality combinations and missing ratios, rather than relying on specific missing patterns. Second, synthesis and segmentation should be jointly optimized in end-to-end pipelines to better align generated image quality with downstream segmentation performance. Third, uncertainty modeling and reliability calibration should be strengthened to provide clinically meaningful confidence estimates and risk-aware outputs. Fourth, stronger domain generalization and domain adaptation methods are required to improve robustness across institutions, scanners, and patient populations. Fifth, integrating large multimodal models with medical priors (e.g., anatomical constraints and pathology-aware priors) could improve generalization in small-sample and high-missingness settings. Sixth, evaluation protocols should go beyond Dice and include boundary-sensitive metrics, inference latency, model size, and computational cost to better reflect real deployment needs. Finally, greater emphasis on reproducibility and clinical translation, including open-source implementations, standardized preprocessing pipelines, and prospective validation, is essential to bridge the gap between algorithm development and practical clinical adoption.

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