# Progress in Neuro-Oncology

## Challenges and Advances in Brain Tumor Segmentation

Samah M. Morsi, MD, MSc

Postdoctoral research fellow in Computational Imaging

# In Brain Tumor Imaging

# 5 Game-Changing Questions?"

**How** does the addition of a FLAIR sequence to T1CE significantly enhance tumor visualization, potentially revolutionizing pre-operative planning?

**Can** deep learning models accurately identify enhancing brain tumors without the need for contrast agents, offering a safer and more cost-effective approach?

**Why** is the ability to effectively segment tumors with limited data sets a game-changer in clinical practice and medical research?

**What are** the key advantages and challenges of using single-sequence models for brain tumor segmentation, and when are they most beneficial?

**How** do automated segmentation models demonstrate strong generalizability across different imaging scenarios, potentially transforming clinical response assessment in situations with incomplete data?

# Comprehensive Imaging Modalities for Accurate Brain Tumor Segmentation

+ To perform accurate brain tumor segmentation, a combination of various medical imaging data is typically required:

1. **T1-weighted (T1) Imaging**: Shows brain anatomy.
2. **T2-weighted (T2) Imaging**: Differentiates brain tissues.
3. **T1-weighted with Gadolinium Contrast Enhancement (T1CE) Imaging**: Highlights tumor-enhancing regions.
4. **Fluid Attenuated Inversion Recovery (FLAIR) Imaging**: Suppresses cerebrospinal fluid, aiding tumor visibility.
5. **Diffusion-Weighted Imaging (DWI)**: Reveals tumor cellularity.
6. **Perfusion Imaging**: Assesses tumor blood flow.
7. **Magnetic Resonance Spectroscopy (MRS)**: Analyzes tissue chemistry.
8. **Computed Tomography (CT) Imaging**: Provides cross-sectional brain images.
9. **Positron Emission Tomography (PET) Imaging**: Offers metabolic insights.
10. **Multi-modal Fusion**: Combines different modalities for more accurate segmentation.

# Introduction

**Heterogeneity in Brain Tumors**: Progress in neuro-oncology is hindered by the marked heterogeneity, including genetic, pathological, and clinical variations, in brain tumors.

**Need for Rich Data**: To predict individual patient outcomes and treatment susceptibilities, large-scale, fully-inclusive, and richly phenotyped data, including imaging, are required.

**Real-World Data Challenges**: Data collected in routine clinical practice often suffer from quality degradation due to real-world clinical care constraints.

**Machine Learning for Imaging**: Machine learning, particularly in the domain of imaging, is considered a potential solution to address these challenges.

# Introduction

Segmentation models can accurately detect enhancing tumors even without contrast-enhancing imaging, achieving high accuracy.

The additional MR sequences, especially contrast-enhanced ones, may offer marginal benefits, potentially reducing cost and risk to patients

The ability to quantify enhancing tumors without contrast administration prompts reconsideration of its necessity in certain cases.

Brain tumor segmentation models excel with incomplete MRI sequences commonly encountered in clinical practice, promising enhanced precision in tumor management.

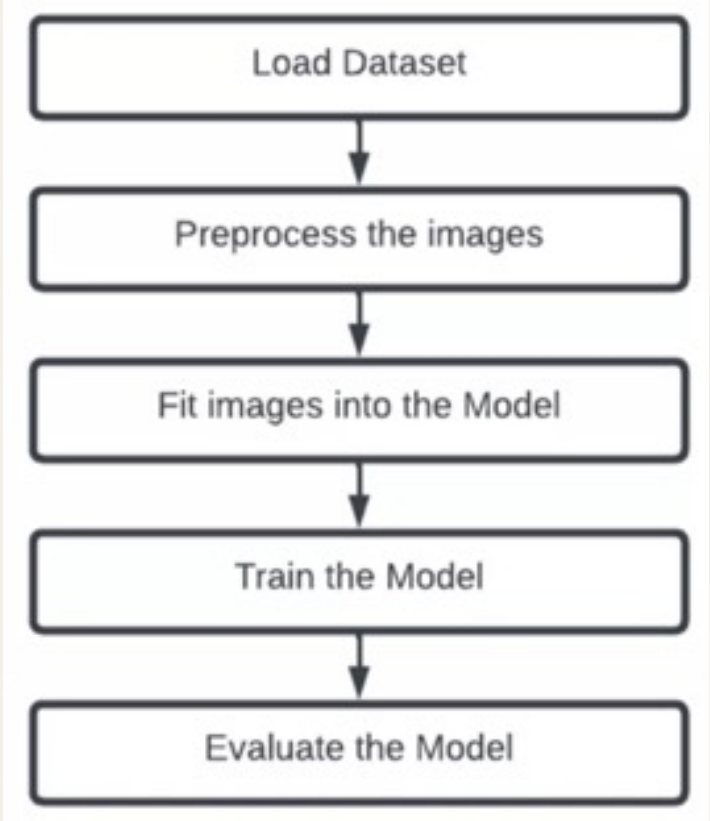
# Challenges

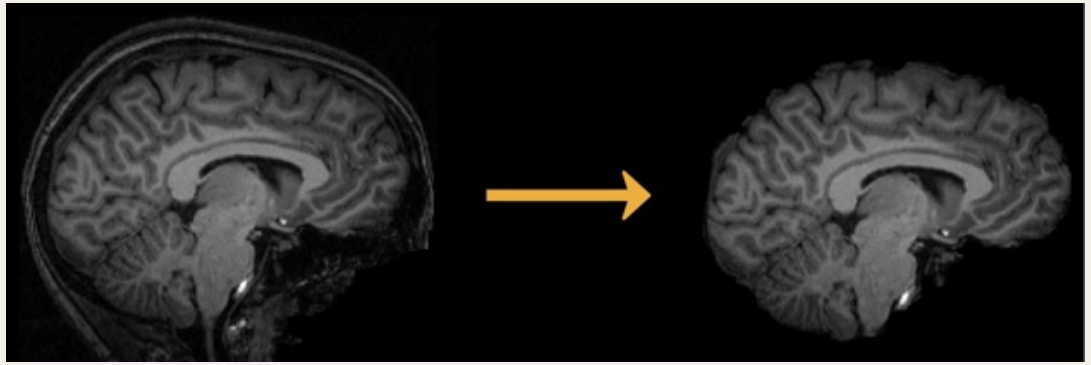
Incomplete data in clinical practice results from various factors, including patient contraindications, image artifacts, and acquisition constraints.

Motion artifact prevalence in MRI studies is reported to be 7.5% in outpatient and 29.4% in inpatient studies, with a significant economic impact.

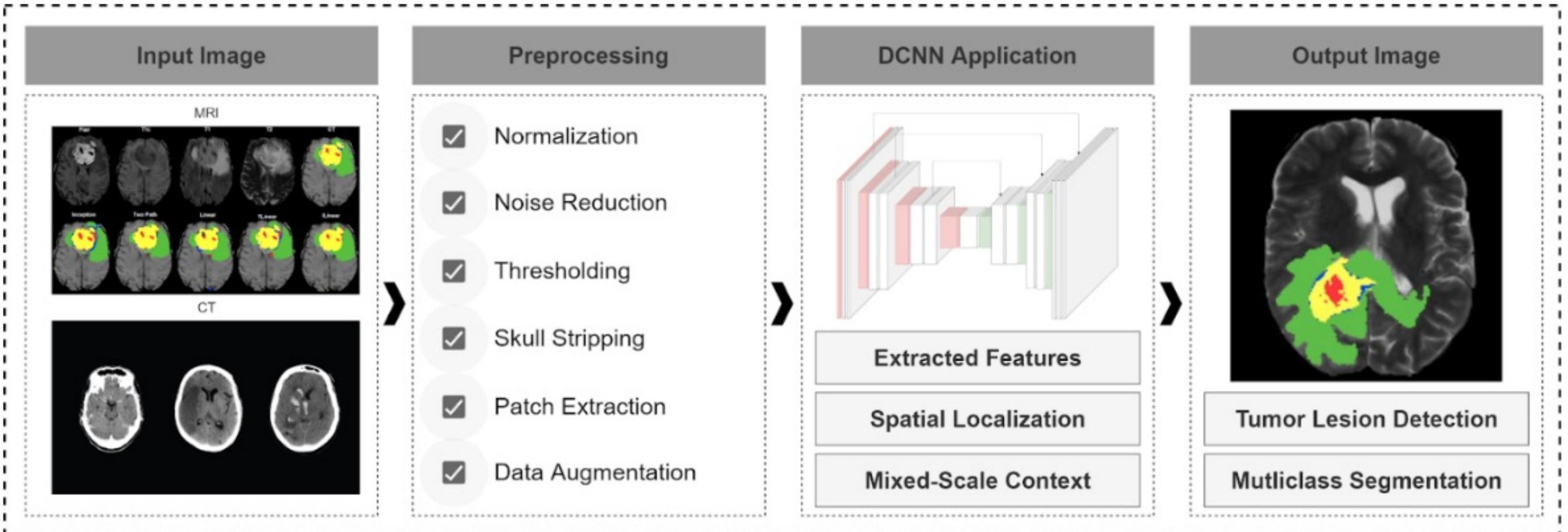
The practical utility of tumor segmentation in clinical settings with incomplete data is unknown.

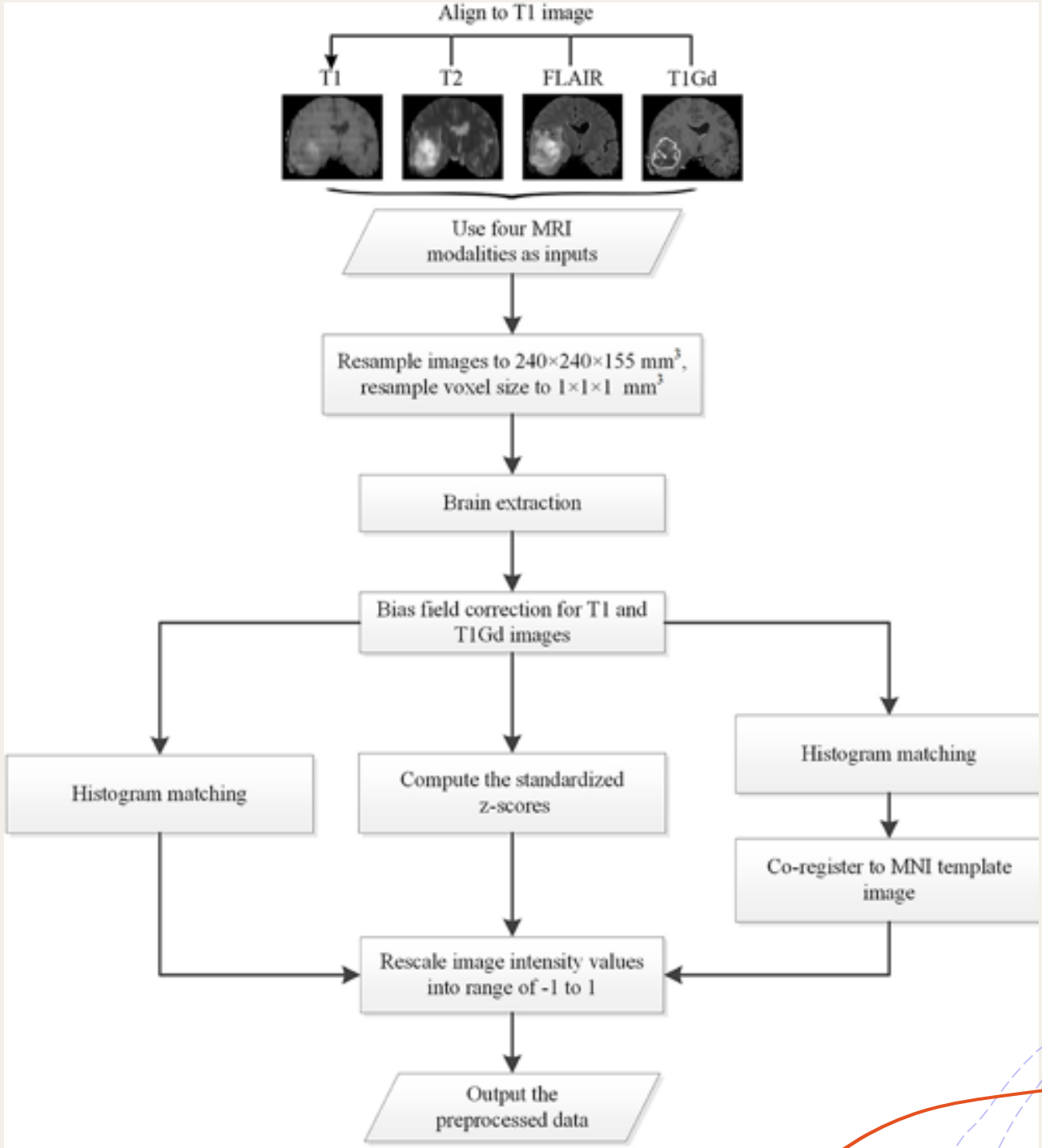
# Brain Tumor Segmentation and Validation

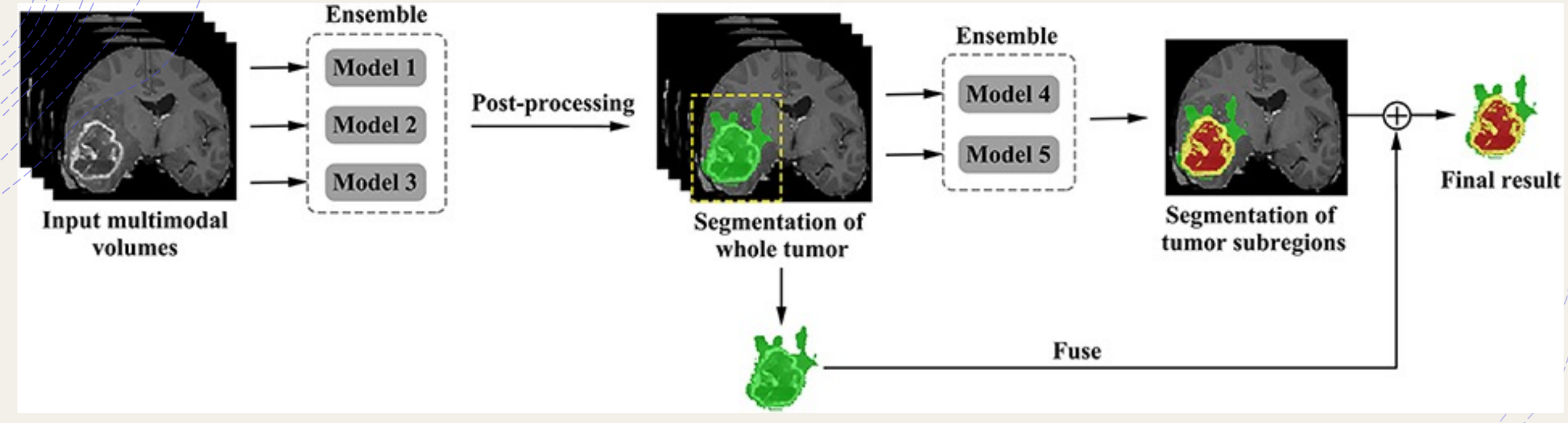


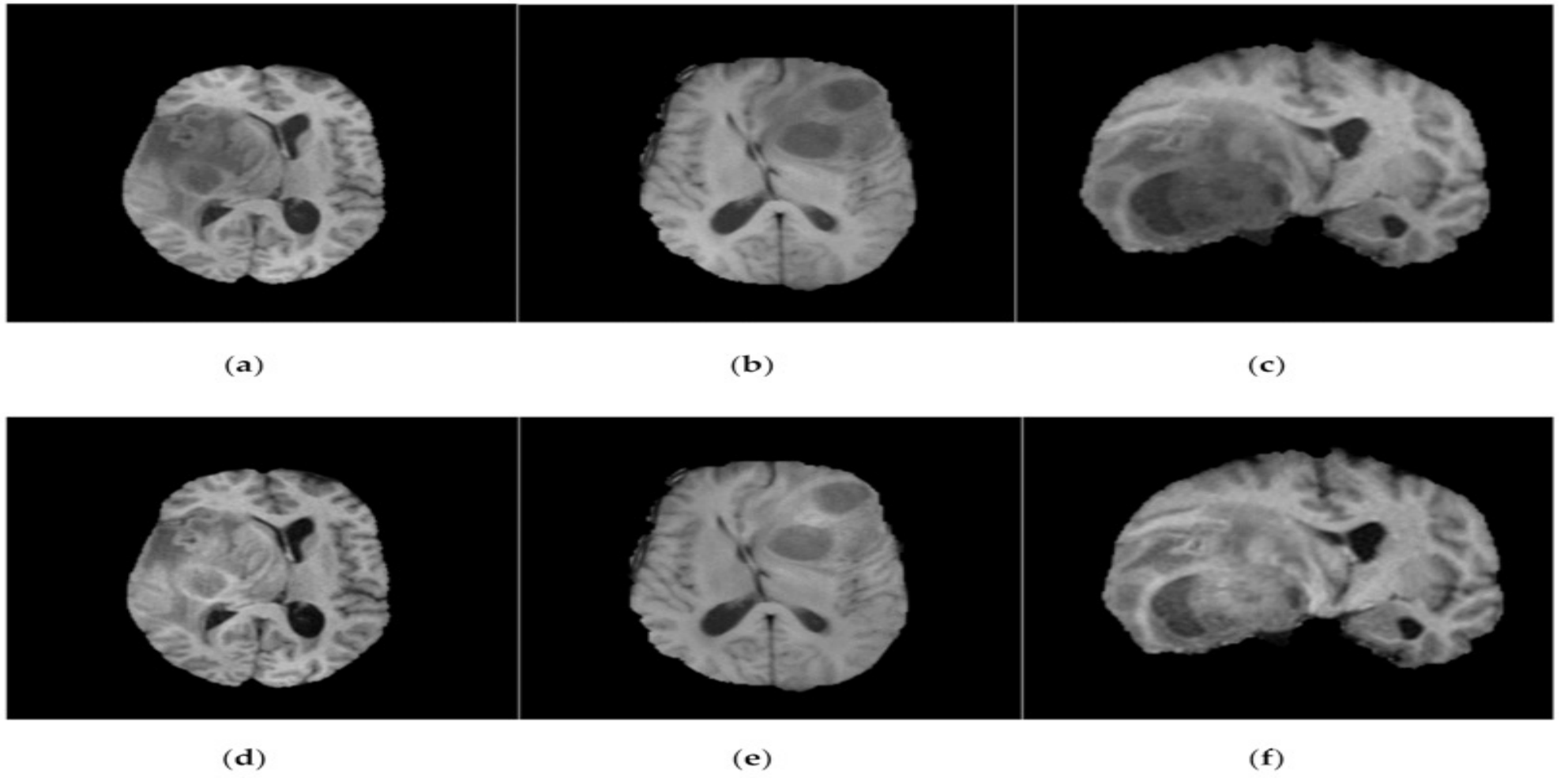
+ Typical brain tumor segmentation Architecture with the following high-level steps:
+ 1. Input: magnetic resonance (MRI) and computed tomography(CT) scans are input into the model;
+ 2. Preprocessing: apply several techniques to normalize images, remove noise, and filter irrelevant components
+ 3: Deep Convolutional Neural Network (DCNN)Application: The preprocessed dataset is fed into a DCNN model the extract features for segmentation, with localization a key component;
+ 4. Output Images: Specifies the result of the segmentation model.




Align to T1 image
T1
T2
FLAIR
T1Gd
Use four MRI modalities as inputs
Resample images to 240×240×155 mm³, resample voxel size to 1×1×1 mm³
Brain extraction
Bias field correction for T1 and T1Gd images
Histogram matching
Compute the standardized z-scores
Histogram matching
Co-register to MNI template image
Rescale image intensity values into range of -1 to 1
Output the preprocessed data


Ensemble
Model 1
Model 2
Model 3
Input multimodal volumes
Post-processing
Segmentation of whole tumor
Ensemble
Model 4
Model 5
Segmentation of tumor subregions
Final result
Fuse

# Sample images from BraTS-2018 dataset before and after bias field correction



# Steps to overcome challenges of incomplete data “Relative study”

**Data Source:**

1.Used diverse brain tumor MRI scans from the BraTS 2021 challenge.

**Data Preprocessing:**

1.Aligned images and removed skull information.

**Lesion Segmentation:**

1.Combined top-ranked BraTS algorithms and manual refinement by neuroradiologists.

**Training Data:**

1.Employed a training set of 1251 individuals with 5004 labeled images.

**Additional Validation:**

1.Included 50 individuals with glioblastoma from 2006 to 2021 for added diversity.

**Challenging Cases:**

1.Among the 50 participants, 10 had post-operative imaging and tumor recurrence, increasing complexity.

**Super-Resolution:**

1.Used super-resolution to enhance image quality when volumetric data was lacking.

**Lesion Labeling:**

1.Manually labeled lesions using ITK-SNAP and semi-automated tools.

**Tumor Annotations:**

1.Employed established labels, including gadolinium-enhancing tumor, peritumoral edema/invaded tissue, and non-enhancing tumor/necrotic tumor core.

**Detailed Tissue Description:**

1.Provided detailed descriptions of tissue components, such as enhancing tumor regions, non-enhancing tumor/necrotic tumor core, and edema/invaded tissue, each with specific MRI characteristics.

# Steps to overcome challenges of incomplete data “Relative study”

**Model Selection:** Chose nnU-Net, known for its strong performance in biomedical image segmentation.

**Automated Configuration:** nnU-Net automatically handles preprocessing, architecture selection, training, and post-processing.

**Specialized Architecture:** Utilized a self-configuring 3D U-Net architecture tailored for image processing.

**Optimization Setup:** Employed stochastic gradient descent with a polynomially decaying learning rate (starting at 0.01).

**Loss Function:** Used a combined loss function integrating the Sørenson-Dice coefficient and cross-entropy.

**Data Augmentation:** Applied augmentation techniques (rotations, scaling, noise, blur, brightness, contrast, gamma correction) during model training.

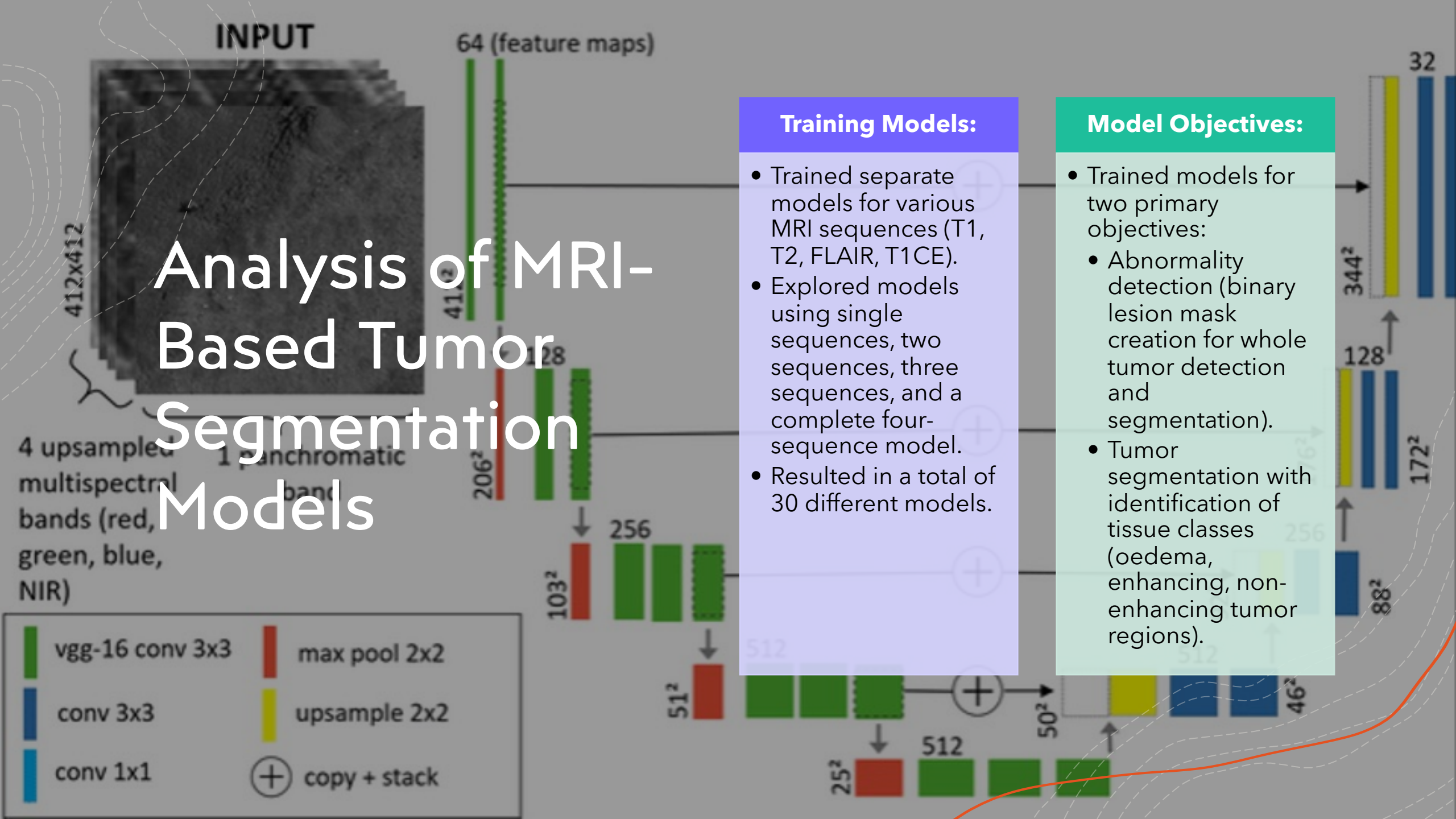
**Training Details:** Trained the model for 1000 epochs with foreground oversampling to address class imbalances.

**Cross-Validation:** Utilized 5-fold cross-validation for robust model performance assessment.

**Evaluation Data:** Assessed the model using data from the BraTS 2021 challenge as well as external/international datasets.

| Aspect | nnU-Net | Standard U-Net |
| --- | --- | --- |
| Architectural Diversity | Adapts to dataset and task complexity | Single fixed architecture |
| Architecture Selection | Automatic based on data | Manual selection and tuning |
| Training Efficiency | Longer training due to complexity | Faster training due to simplicity |
| Generalization | Better across diverse datasets | Depends on manual tuning and expertise |
| Flexibility | Highly flexible for different tasks | Designed primarily for segmentation |
| Preprocessing | Often requires minimal preprocessing | May need more preprocessing effort |
| Implementation | Potentially more complex to implement | Simpler to implement with a single arch |
| Community Support | Smaller but growing community support | Larger, well-established community |

# Analysis of MRI-Based Tumor Segmentation Models




## Training Models:

- Trained separate models for various MRI sequences (T1, T2, FLAIR, T1CE).
- Explored models using single sequences, two sequences, three sequences, and a complete four-sequence model.
- Resulted in a total of 30 different models.

## Model Objectives:

- Trained models for two primary objectives:
  - Abnormality detection (binary lesion mask creation for whole tumor detection and segmentation).
  - Tumor segmentation with identification of tissue classes (oedema, enhancing, non-enhancing tumor regions).

## Performance Metrics:

Evaluated model performance using the Sørenson-Dice coefficient, a common research metric.

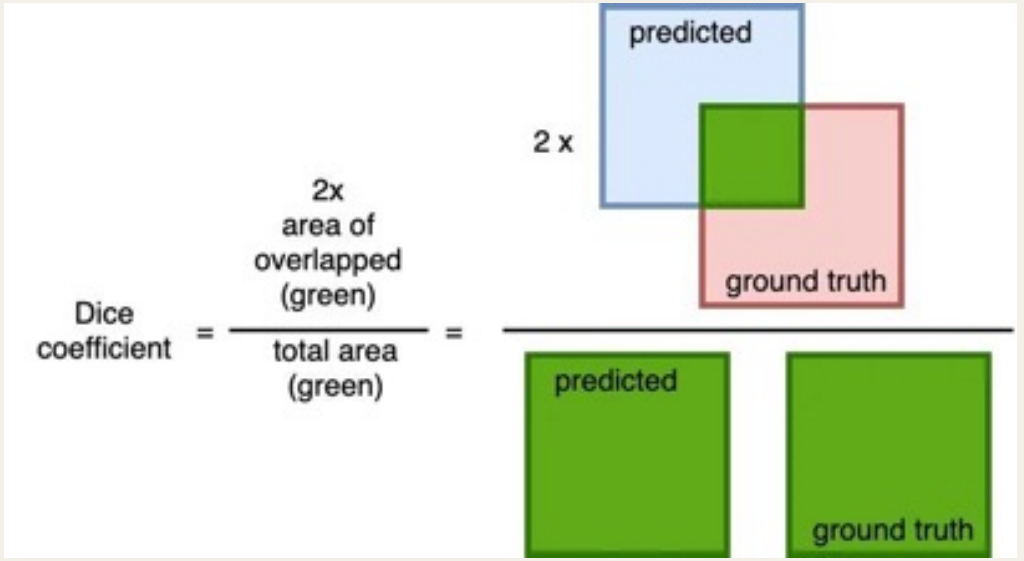
Dice coefficient formula: $Dice = 2(TP)\ .\ (TP + FP) + (TP + FN)$.

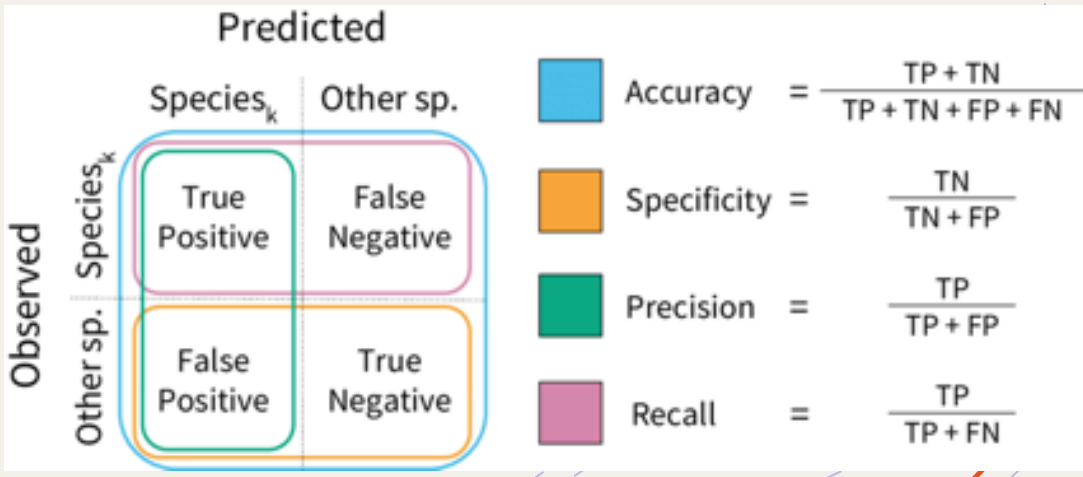
## Additional Performance Metrics:

Utilized various other metrics, including accuracy, false discovery rate, false negative rate, false omission rate, false positive rate, negative predictive value, precision, and recall.

Calculated metrics for both the entire tumor and its separate tissue components.

Provided 95% confidence intervals for these metrics.



# Analysis of MRI-Based Tumor Segmentation Models

| | |
|---|---|
| **Regression Models:** | Developed regression models to relate ground truth tumor volumes to model predictions.<br>Reported the coefficient of determination (R2). |
| **Acquisition Time Comparison:** | Compared model performance with the acquisition times of contemporaneous imaging protocols.<br>Measured the time it takes to acquire each imaging sequence. |
| **tSNE Analysis:** | Applied t-distributed stochastic neighbor embedding (tSNE) to contrast-enhancing components of lesions in the BraTS dataset.<br>Created a two-dimensional representation of lesions to highlight their high-dimensional similarities and differences. |
| **Visualization:** | Visualized variation in lesion volume and Sørenson-Dice coefficient in relation to lesion morphology. |
| **Supplementary Material:** | Provided detailed 95% confidence intervals and supplementary material for reported metrics. |

# “Incremental Performance Gains with Sequential Addition" effectively conveys the idea that performance improves as sequences are added incrementally

**Evaluation Method**: The models are evaluated using Dice coefficients to measure segmentation accuracy.

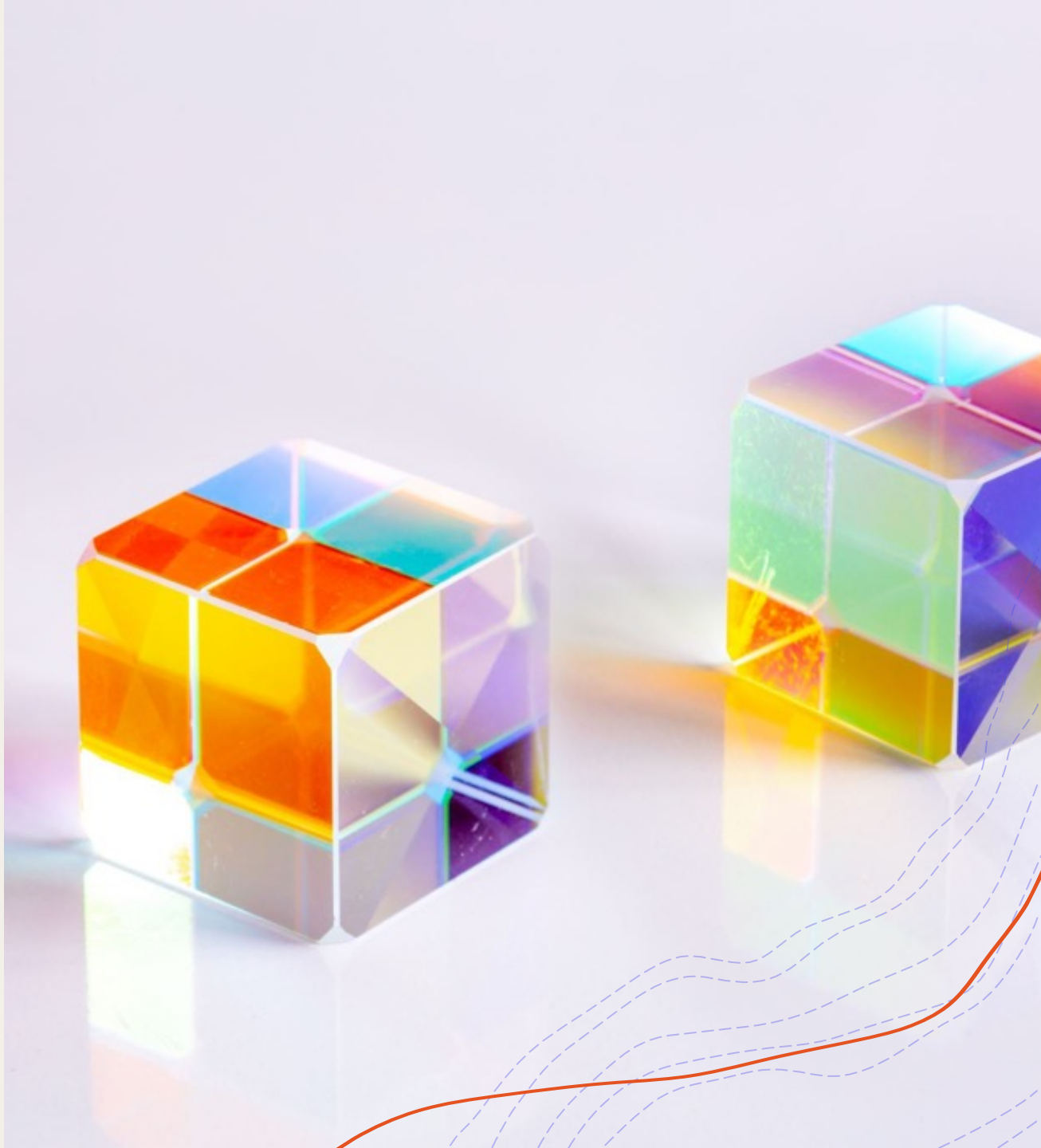
**Whole Tumor Segmentation**:

Dice coefficients range from 0.907 (single sequence) to 0.945 (complete sequence set).
Dice coefficients vary from 0.701 to 0.891.

**Segmentation of Different Tumor Components**:

Poor performance in non-enhancing tumor segmentations, especially in single-sequence models (T1, T2, FLAIR) and two/three-sequence

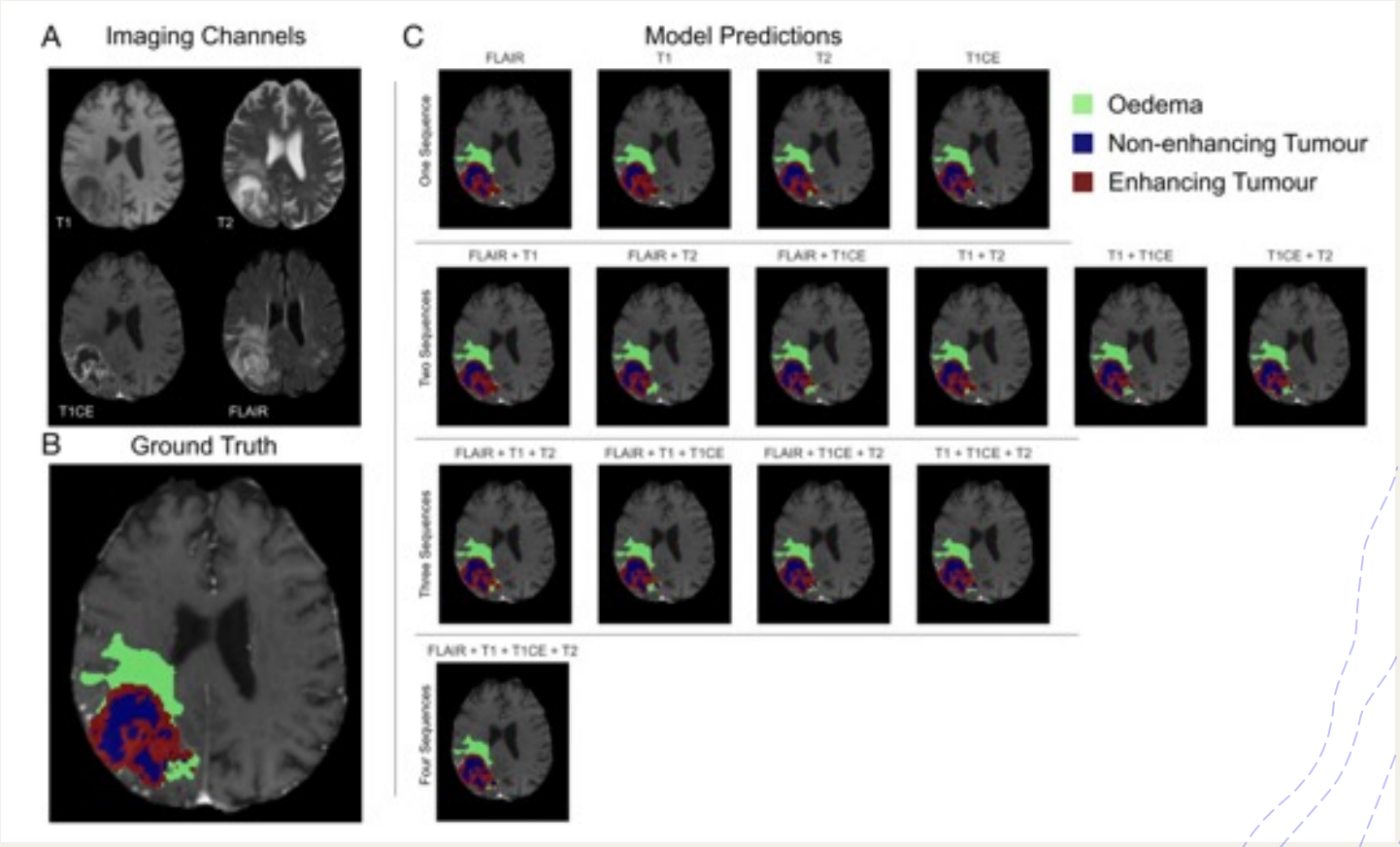
**No Overfitting**: No evidence of model overfitting based on training/validation curves.



# “Incremental Performance Gains with Sequential Addition"

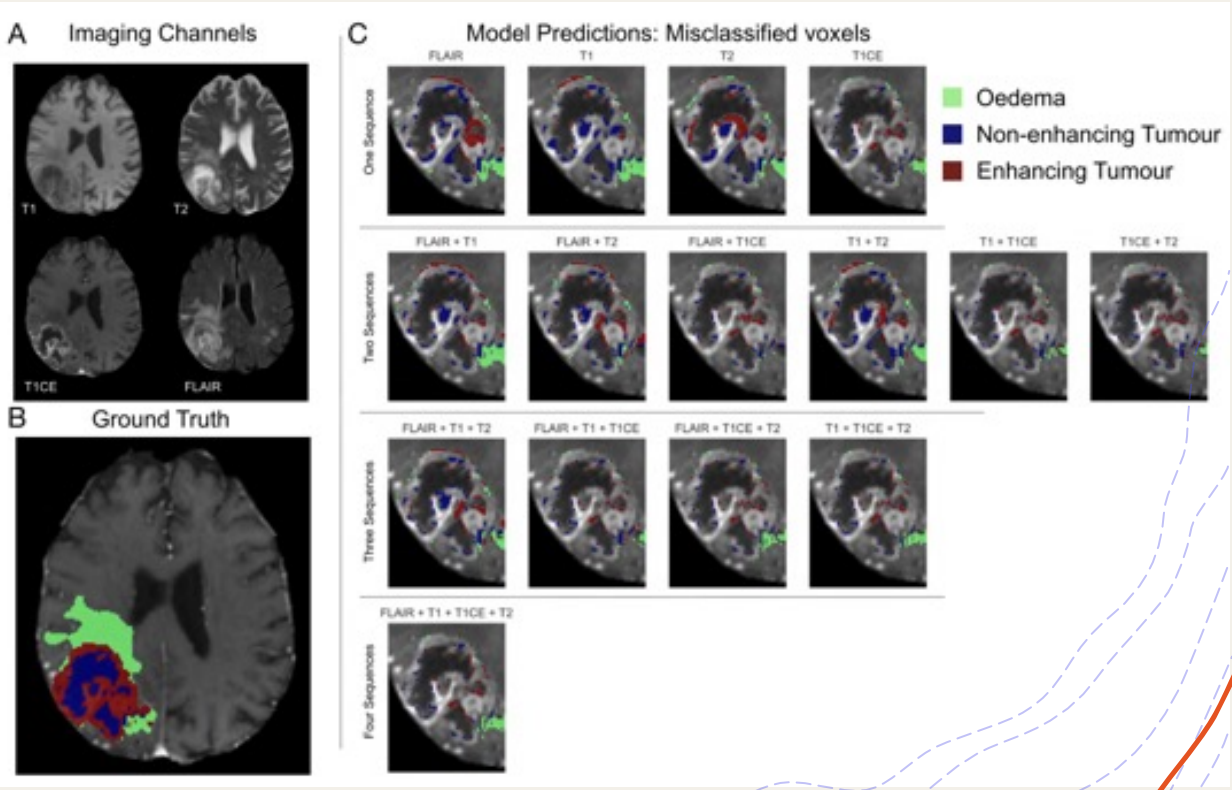
**Image Segmentations**: Image segmentations across all models show excellent lesion coverage with minimal error.

**Additional Metrics**: Model accuracy, false discovery rate, false negative rate, false omission rate, false positive rate, negative predictive value, precision, and recall were evaluated.



# Balancing Acquisition Time and Segmentation Quality

- Examined acquisition times for different imaging sequences.
- Measured improved model accuracy using Dice coefficient per scanning minute.
- Discovered certain sequence combinations enhance segmentation performance.
- Single volumetric T1CE took 3.1 minutes, achieved Dice coefficient 0.908.
- Adding FLAIR increased time to 4.9 mins, improved Dice to 0.943.
- Three-sequence (FLAIR + T1CE + T2) without pre-contrast T1 reduced time by 33% (9.48 to 6.38 mins).
- Omitting pre-contrast T1 had issues in delineating contrast (e.g., haemorrhage).



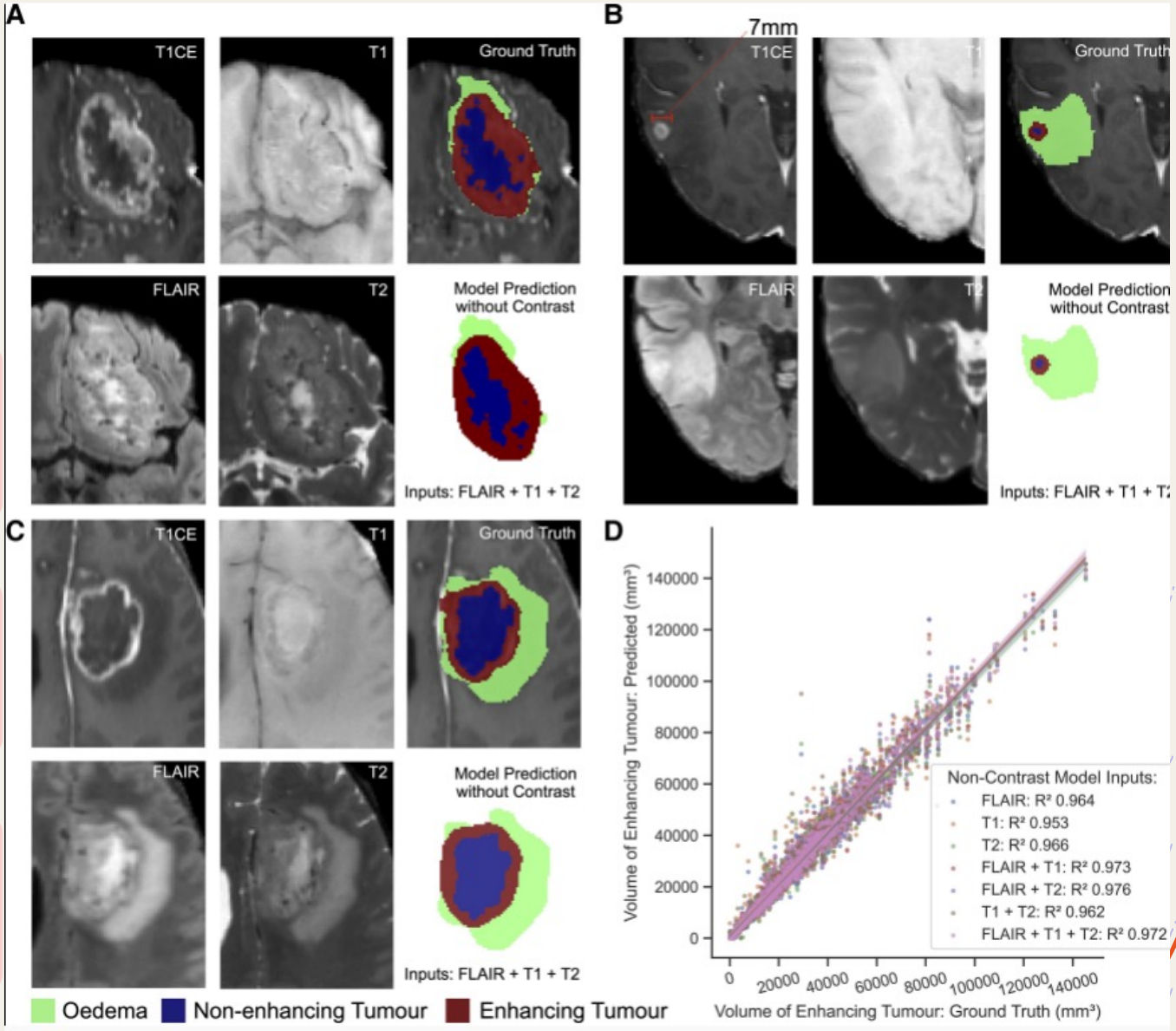
# Segmenting Enhancing Tumors in Medical Images without Contrast

**Contrast-Enhanced T1 Sequence**: Models without the contrast-enhanced T1 sequence can still identify the enhancing tumor component with Dice coefficients ranging from 0.756 to 0.790.

**Enhancing Tumor Volume**: The volume of enhancing tumors strongly correlates with model predictions, even when contrast-enhanced imaging is not used.

**t-SNE Analysis**: t-SNE-derived low-dimensional representations of lesions do not show a clear relationship between lesion anatomy and segmentation performance.

**Linear Regression**: Linear regression analysis reveals a significant correlation between the volume of enhancing tumors and model predictions, even in the absence of contrast-enhanced imaging.




Examples of segmenting enhancing tumors without contrast, including cases with small enhancing components.

# "International Clinical Validation of Segmentation Models"

**Evaluation of Models**: Assess model performance on a group of 50 patients with varying scans, both pre- and post-operative.

**Reproducibility**: Confirm that model performance is consistent using cross-validation (Dice coefficients highly correlated).

**Effect of Imaging Modalities**: Models using multiple scan types perform better than those relying on a single scan type (e.g., T1 or T2).

**Tissue Class Segmentation**: Models accurately classify tumor subclasses (non-enhancing, enhancing, and edema) for further refinement.

**Performance Comparison**: Compare model performance with and without four imaging sequences using revised ground truth data. Results are consistent across different datasets.

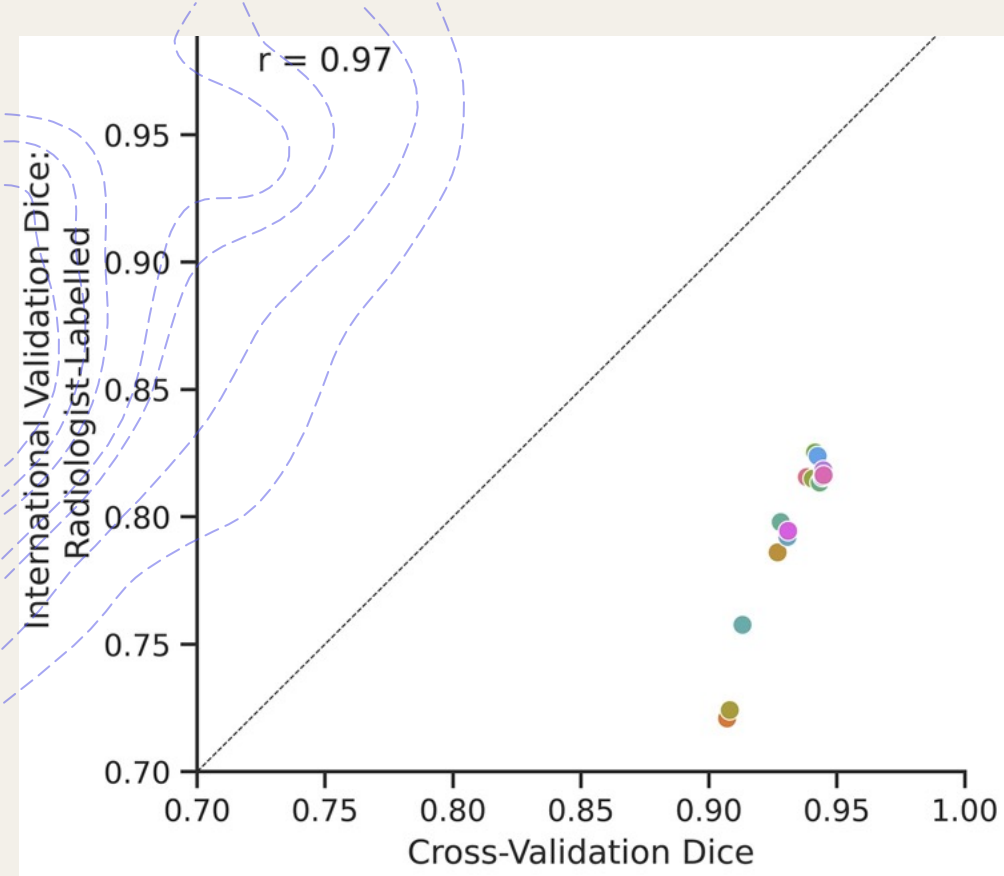
# "International Clinical Validation of Segmentation Models"

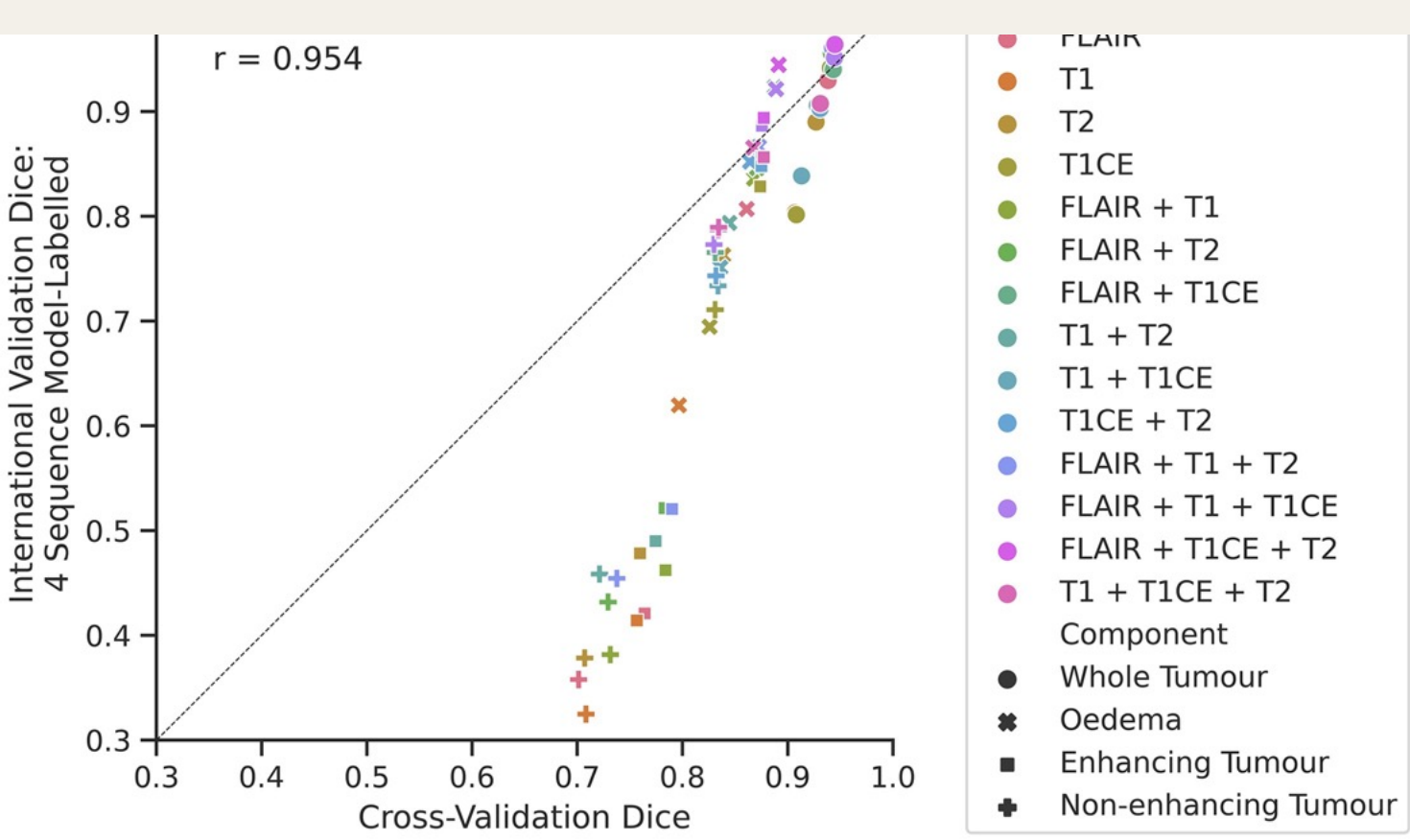
**Lesion Volumetry**: Apply the segmentation pipeline to track lesion volume changes over time for a patient with variable image quality (2010-2015).

**Image Quality**: Note that despite variations in image quality, the segmentation model consistently delineates tissue components even in suboptimal images.

**Longitudinal Imaging Example**: Figure 8 illustrates a single case with longitudinal imaging, displaying time on the x-axis and lesion volume on the y-axis. Different scanning sessions are color-coded for tumor components.

**Recognition of Surgical Cavity**: The model correctly identifies the surgical cavity as distinct from the lesion, even without being trained on post-operative images.




**Scatterplot A:** Strong correlation between radiologist-labeled lesions and model predictions for whole tumor segmentations, highlighting model accuracy in delineating tissue classes.

**Scatterplot B:** Strong relationship between model performance on the validation set and when re-evaluated on their own data, using the complete four-sequence model as ground truth.

# Take home message

**Enhance Tumor Visualization**:

Add FLAIR sequence to T1CE imaging.

Improves contrast and highlights edema areas.

**Utilize Deep Learning Models**:

Use deep learning to identify tumors without contrast agents.

Enhances safety, reduces costs, and increases patient compliance.

**Effective Tumor Segmentation**:

Develop models that can segment tumors with limited data.

Maximizes data usage, reduces imaging requirements, and speeds up diagnosis.

**Single-Sequence Models**:

Consider single-sequence models for quick assessments.

Ideal for situations where complex multi-sequence models are unnecessary.

**Automated Segmentation for Generalization**:

Implement automated segmentation models for generalizability.

Enhances clinical response assessment in various scenarios, even with incomplete data.

# References


1. James K Ruffle, Samia Mohinta, Robert Gray, Harpreet Hyare, Parashkev Nachev, Brain tumour segmentation with incomplete imaging data, Brain Communications, Volume 5, Issue 2, 2023, fcad118, https://doi.org/10.1093/braincomms/fcad118
2. Ruffle JK, Mohinta S, Pombo G, et al. Brain tumour genetic network signatures of survival. arXiv. 2023.
3. Peng J, Kim DD, Patel JB, et al. Corrigendum to: Deep learning-based automatic tumor burden assessment of pediatric high-grade gliomas, medulloblastomas, and other leptomeningeal seeding tumors. Neuro Oncol. 2021;23(12):2124–2124.
4. Xue J, Wang B, Ming Y, et al. Deep learning–based detection and segmentation-assisted management of brain metastases. Neuro Oncol. 2020;22(4):505–514.
5. Lu S-L, Xiao F-R, Cheng JC, et al. Randomized multi-reader evaluation of automated detection and segmentation of brain tumors in stereotactic radiosurgery with deep neural networks. Neuro Oncol. 2021;23(9):1560–1568.
6. Lenchik L, Heacock L, Weaver AA, et al. Automated segmentation of tissues using CT and MRI: A systematic review. Acad Radiol. 2019;26(12):1695–1706.
7. Suetens P, Bellon E, Vandermeulen D, et al. Image segmentation: Methods and applications in diagnostic radiology and nuclear medicine. Eur J Radiol. 1993;17(1):14–21.
8. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3):839–851.
9. Menze BH, Jakab A, Bauer S, et al. The multimodal brain tumor image segmentation benchmark (BRATS). IEEE Trans Med Imaging. 2015;34(10):1993–2024.
10. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. Radiology. 2009;252(1):263–272.
11. McNitt-Gray MF, Kim GH, Zhao B, et al. Determining the variability of lesion size measurements from CT patient data sets acquired under “no change” conditions. Transl Oncol. 2015;8(1):55–64.