Università di Brescia

Dipartimento di Scienze Cliniche e Sperimentali

Dottorato di Ricerca in
«Intelligenza Artificiale in Medicina e Innovazione nella Ricerca clinica e metodologica»

Coordinatore: Prof. Domenico Russo

Deep Learning–Guided Prediction and Differentiation of Tumor Progression and Radiation Effects After Stereotactic Radiosurgery for Brain Metastases (AI-BRAINMET)

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PRIMARY OBJECTIVE

Leveraging the latest advancements in artificial intelligence,
we aim to develop an innovative DL model using MRI sequences and other data to achieve the following key objective:

1. **Predict the response of BMs to SRS**:
   Analyze pre-treatment MRI, planning RT, clinical and laboratory data to identify patterns correlating with treatment outcomes.

SECONDARY OBJECTIVES

1. **Differentiate between TP, and PTREs following SRS for BMs**:

   Use pre- and post-treatment MRI, RT, and clinical and laboratory data to make differential diagnoses (DD) between TP or PTREs such as PsP and RN.

3. **Identify RT planning parameters associated with improved treatment response:**

   Determine which RT planning characteristics (e.g., fractions, dose per fraction, dose distribution, conformity, gradient index) correlate with better clinical and radiological outcomes, enabling personalized optimization of future SRS treatment planning.

3. **Automatic contouring:**

   Build an automatic contouring model for BMs in planning MRI to support and standardize lesion segmentation, with the potential to additionally perform whole-brain segmentation to preserve anatomical context and tumor microenvironment features.

3. **Develop an open-source multimodal research database:**

   Create an accessible, structured, and privacy-compliant online repository aggregating imaging, clinical, RT planning, and liquid biopsy data to foster collaboration and support future research in AI-driven oncology and radiomics.

Developmental Pathways

1. Systematic Review and Meta-analysis of Deep Learning Applications in External Beam Radiation Therapy (EBRT) for Brain Metastases

Knowledge generation → understanding the state of the art and deriving methodological insights

2. Development of a Preliminary Deep Learning Framework Based on Publicly Available Datasets

Proof-of-concept model development → initial architecture and identification of limitations

3. Development and Validation of a Clinical Deep Learning Framework Based on a Multi-institutional Dataset

Clinical translation → model development, external validation, and generalizability

1. Systematic Review and Meta-analysis

- Conduct a systematic review, and when feasible a meta-analysis, of Deep Learning applications in External Beam Radiation Therapy (EBRT) for brain metastases.
- Perform a comprehensive assessment of current clinical applications and model performance reported in the literature.
- Extract and harmonize homogeneous data across studies to enable quantitative analyses.
- Provide a state-of-the-art overview of DL approaches and estimate the performance achieved by currently available models.
- Investigate methodological and clinical factors influencing model performance, including dataset characteristics, imaging modalities, annotation strategies, and validation procedures.
- Exploit the evidence generated from the literature analysis to guide the development and optimization of our own deep learning frameworks.

1. Systematic Review and Meta-analysis: Current Status

Completed

1. Research question and objectives defined
2. PICOS framework established
3. Search strategy finalized and Database interrogation completed
4. PROSPERO protocol drafted and ready for registration
5. Spreadsheet for data extraction completed

1. Systematic Review and Meta-analysis: Current Status

1. Research question and objectives defined

What is the current evidence regarding the application, performance, and generalizability of DL models in EBRT for patients with BMs, and which methodological or clinical factors influence their variations in performance?

Review objectives

Primary objective

1. To systematically identify, evaluate, classify, and synthesize the current applications & performance of DL models in EBRT for BMs.

Secondary objectives

1. To investigate methodological and clinical factors potentially associated with variations in model performance and generalizability.
2. Where feasible, to quantitatively synthesize performance metrics across comparable studies and clinical tasks.

1. Systematic Review and Meta-analysis: Current Status

2. PICOS framework

Component	Description
Population	Patients with brain metastases undergoing EBRT
Intervention	Imaging-based Deep Learning models
Comparators	Other DL models, conventional methods, expert evaluation
Outcomes	Clinical applications and model performance metrics (DSC, AUC, Accuracy, Sensitivity, Specificity, HD, etc.)
Study design	Original peer-reviewed studies (2015–2026)

1. Systematic Review and Meta-analysis: Current Status

3. Search strategy finalized & Database interrogation

Component	Description
Time frame	January 2015 – 2026
Databases searched	PubMed/MEDLINE, Scopus, Web of Science, CINAHL, Cochrane Library, Ovid-LWW
Concept 1: Artificial Intelligence	Deep Learning, CNN, U-Net, Transformers, Neural Networks
Concept 2: Radiation Therapy	EBRT, Radiotherapy, SRS, SRT, Gamma Knife, CyberKnife, LINAC, Proton Therapy
Concept 3: Disease	Brain metastases, intracranial metastases, secondary brain tumors
Search strategy	(Deep Learning terms) AND (Radiotherapy terms) AND (Brain metastases terms)
Language restriction	English
Study period	2015–2026
Records retrieved	PubMed (102), Scopus (98), Web of Science (170), CINAHL (46), Cochrane (6), Ovid-LWW (7)
Total records identified	**429**

1. Systematic Review and Meta-analysis: Current Status

3. Search strategy finalized & Database interrogation

Database	Results	Dedup_EndNote	Dedup_Py/pan	Output
Scopus	98	-37	-13	48
PubMed	102	-72	-8	22
Web Of Science	170	0	-32	138
CINAHL	46	-12	-9	25
OVID_LWW	7	-2	-2	3
Cochrane	6	-3	-2	1
tot.	429	-126	-66	**237**

1. Systematic Review and Meta-analysis: Current Status

4. Spreadsheet for data extraction

Domain	Variables Extracted
Study Characteristics	Authors, year, DOI, country, sample size, EBRT platform, study scope
Clinical and Imaging Data	Input modalities, MRI sequences, time points, ground truth, outcome definitions
Deep Learning Models	Clinical task, model architecture, training strategy, augmentation, explainability
Dataset Characteristics	Training/validation/test cohorts, class distribution, multicenter design, raw data availability
Validation Strategy	Internal validation, external validation, cross-validation
Performance Metrics	DSC, HD, AUC, accuracy, sensitivity, specificity, precision, recall, F1-score, MAE, etc.
Comparative Analysis	Reference methods, competing models, best-performing factors
Open Science Practices	Code availability, public datasets
Risk of Bias Assessment	PROBAST-AI domains and overall judgment

2. Preliminary Deep Learning Framework Based on Publicly Available Datasets: Current Status

- Identify and curate a preliminary dataset from publicly available resources.
- Develop a DL-based automatic contouring model for brain metastases on planning MRI, capable of detecting lesions of all sizes and generalizing across multi-center imaging acquisitions.
- Extend the segmentation framework to whole-brain delineation to preserve anatomical context and tumor microenvironment information.
- Design an initial DL architecture to address prediction and differentiation tasks.
- Evaluate the model performance to identify current limitations and highlight areas requiring further improvement.

2. Preliminary Deep Learning Framework Based on Publicly Available Datasets: Current Status

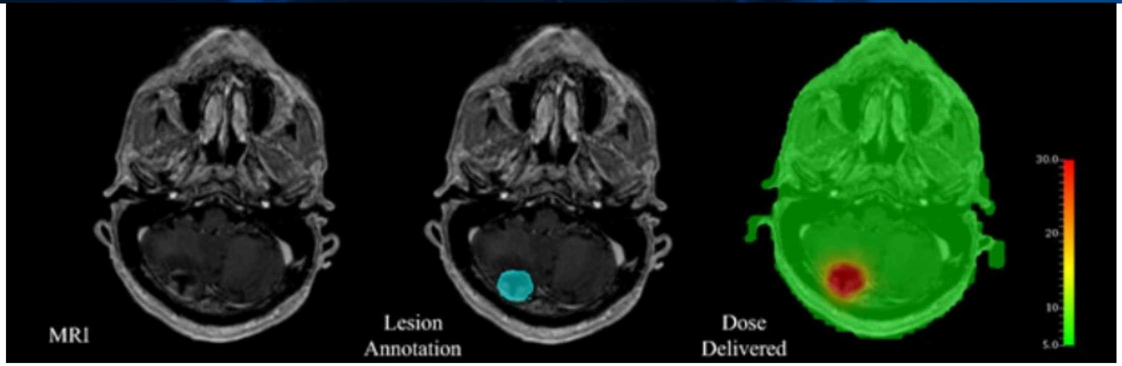
Completed

1. Public dataset Identification
2. Identification of potential objectives achievable through the available dataset

2. Preliminary Deep Learning Framework Based on Publicly Available Datasets: Current Status

1. Public dataset Identification

NATIONAL CANCER INSTITUTE
CIP Cancer Imaging Program



https://www.cancerimagingarchive.net/collection/brain-tr-gammaknife/#citations

2. Preliminary Deep Learning Framework Based on Publicly Available Datasets: Current Status

1. Public dataset

Feature	Brain-TR-GammaKnife Dataset (TCIA)
Source	The Cancer Imaging Archive (TCIA)
Study design	Retrospective
Institution	University of Mississippi Medical Center (UMMC)
Patients	47 patients
Lesions	244 annotated brain metastases
Sex distribution	21 males, 26 females
Treatment modality	Gamma Knife stereotactic radiosurgery (SRS)
Imaging modality	Pre-treatment T1-weighted contrast-enhanced MRI (1.5T Siemens Magnetom, 1×1×1 mm)
Radiotherapy data	RTStruct, RTDose, treatment sessions
Clinical data	Demographics, diagnosis, treatment information
Follow-up data	Longitudinal MRI follow-up for recurrence assessment
Data format	DICOM, NRRD, XLSX
Annotations	Expert lesion contours
Outcome classes	Stable lesions (221) vs recurrence (23)
Multiple treatment courses	Yes (up to 8 courses/patient)
Dataset size	~11 GB
Additional resources	Baseline algorithm and source code available
Potential AI applications	Segmentation, recurrence prediction, treatment planning, dose-response modeling
Main limitation	Small cohort and marked class imbalance

2. Preliminary Deep Learning Framework Based on Publicly Available Datasets: Current Status

2. Identification of potential objectives achievable through the available dataset

Objective 1	Objective 2
• Multi-task segmentation of the whole brain and individual brain metastases	• Multimodal outcome prediction (True Progression vs Stable Disease)
Whole-brain MRI + lesion delineation	MRI + RTStruct + RTDose + clinical data
Preservation of anatomical context & tumor microenvironment	Identification of imaging & dosimetric predictors of outcome after SRS

3. Development and Validation of a Clinical Deep Learning Framework: Current Status

- Establish a comprehensive multi-institutional clinical dataset to overcome the limitations of publicly available data.
- Develop a novel and enhanced DL architecture leveraging the larger and more representative clinical cohort.
- Incorporate the insights gained from both the systematic review and the preliminary models into the final framework design.
- Perform model fine-tuning and evaluate robustness and generalizability using an independent external cohort.
- Validate the clinical applicability of the proposed approach for reliable deployment in radiation oncology workflows.

3. Development and Validation of a Clinical Deep Learning Framework: Current Status

Completed

1. Participating centers identified
2. Shared project concept defined
3. Regulatory and feasibility assessment initiated
4. Study protocol defined

Regulatory and feasibility assessment

Clinical Trial Center and C.R.E.A. Research Laboratory – ASST Spedali Civili, Brescia

1. Preliminary assessment of study costs and organizational sustainability
2. Evaluation of potential timelines for study approval and initiation
3. Definition of possible study design configurations and their respective regulatory, ethical, and temporal implications

Preliminary assessment of study costs

Tabella riassuntiva dei costi

Voce di costo	Scenario A Retrospettivo osservazionale	Scenario B Prospettico con sangue	Scenario C Prospettico con sangue + liquor
Storage e gestione dati (RM, RT, database, server/cloud, pseudonimizzazione, REDCap)	**10.000–35.000 €**	**10.000–35.000 €**	**10.000–35.000 €**
Trasporto campioni biologici locali (Brescia–Poliambulanza–Niguarda)	—	**2.000–5.000 €**	**3.000–8.000 €**
Trasporto campioni biologici internazionali (USA, Svizzera, Turchia)	—	**10.000–25.000 €**	**15.000–35.000 €**
Storage campioni biologici (freezer, refrigeratori, criostorage)	—	**5.000–15.000 €**	**8.000–25.000 €**
Analisi FT-IR (10–12 €/campione)	—	**25.000–30.000 €**	**50.000–60.000 €**
Copertura assicurativa per procedure aggiuntive (punture lombari)	—	verosimilmente non necessaria	**~10.000 €**
(Personale raccolta dati multicentrica)	*(10.000–25.000 €)*	*(15.000–35.000 €)*	*(20.000–45.000 €)*
(Personale AI / preprocessing / training modelli)	*(20.000–50.000 €)*	*(25.000–60.000 €)*	*(30.000–70.000 €)*

Totali stimati (escludendo personale raccolta dati / AI / preprocessing / training modelli)

Scenario	Totale stimato senza campioni esteri	Totale stimato con gestione campioni esteri
A. Solo retrospettivo osservazionale	**10.000–35.000 €**	non applicabile
B. Retrospettivo + prospettico sangue	**42.000–85.000 €**	**52.000–110.000 €**
C. Retrospettivo + prospettico sangue + liquor	**71.000–138.000 €**	**86.000–173.000 €**

Evaluation of potential timelines for study approval

Regulatory Timeline Scenarios

A. Italian Multicenter Core Project

- Participating centers
  1. ASST Spedali Civili di Brescia
  2. Fondazione Poliambulanza
  3. ASST Niguarda
- Estimated timeline: **~6 months**
- Advantages
  - Faster Ethics Committee approval
  - Simplified regulatory pathway
  - Rapid study activation and data collection
  - Lower organizational complexity

B. International Multicenter Expansion

- Additional centers
  1. Switzerland
  2. Turkey
  3. United States
- Estimated timeline **~2 years**
- Major challenges
  - Data privacy and international data transfer regulations
  - Multinational regulatory requirements
  - International multicenter ethical approvals
  - Increased organizational complexity

Proposed Strategy

Stepwise Implementation

1. Italian multicenter core study

↓

2. Database and AI infrastructure development

↓

3. Progressive international expansion

➢ **Goal**

Accelerate project development while preserving the long-term vision of a fully international multicenter AI-BRAINMET study.

Participating centers → Shared project concept → Core project

Stanford University

EMORY UNIVERSITY

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

UNIVERSITAS STUDIORUM BRIXIAE

OSPEDALE NIGUARDA CA' GRANDA

FONDAZIONE POLIAMBULANZA Istituto Ospedaliero

HUG Hôpitaux Universitaires Genève

KOÇ UNIVERSITY HOSPITAL

Core project

Objective
- **Multimodal Deep Learning model** to predict outcomes in patients with **brain metastases treated with SRS**

Target outcomes
1. True progression (TP)
2. Radiation necrosis (RN)
3. Treatment response:
    - Stable Disease (SD)
    - Partial Response (PR)
    - Complete Response (CR)

Multimodal Inputs

Standard MRI sequences
Clinical variables
RT planning and dosimetric data

Simplified Design
- One or few participating centers
- Single/Two SRS platforms (e.g., CyberKnife, Gamma Knife)
- Single baseline MRI (≤1 week before SRS)
- Follow-up imaging used only for outcome labeling
- Automated whole-brain and lesion segmentation to preserve anatomical context

Feasibility

≈ **400 lesions** expected to be sufficient for model development

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THANK YOU