# Advanced Prediction of GBM Recurrence Via Stem Cell Niche Proximity Estimation Coupled SVM for Personalized Radiotherapy

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# Disclosure and Acknowledgement


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# Glioblastoma multiforme (GBM) General Facts

- GBM is the most common primary brain malignancy in adults.
- Patients' response to standard therapies is unsatisfactory with a dismal 5-year survival of only 7%.
- Nearly all GBM patients recur despite aggressive therapies.
- Radiation played a crucial role for GBM patients with demonstrated survival benefit, but therapeutic outcomes continue to be disappointing.

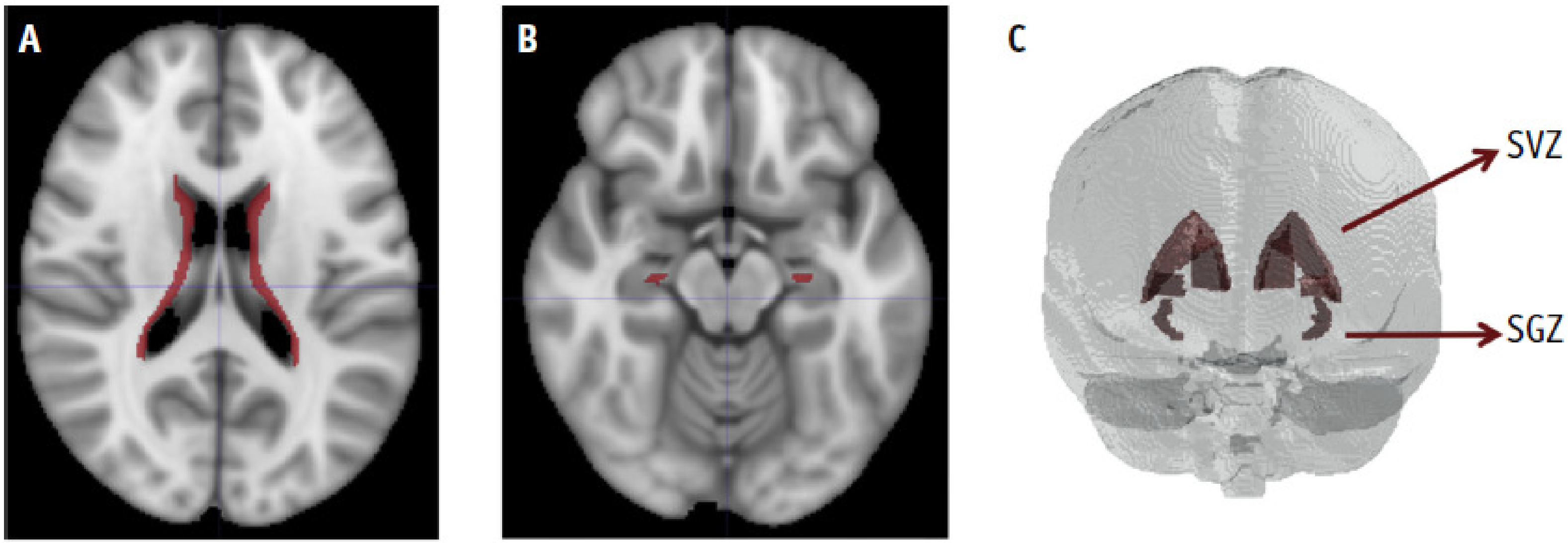
**Algorithms enabling early, and voxel-wise detection of subclinical recurrence are needed for early radiation intervention!**

## Machine Learning and Medical Imaging in RT of GBM

- Machine learning integrated with medical imaging has introduced new perspectives in diagnostics of GBM, mainly through radiomics and radio genomics.
- Radiomics features are extracted to build prediction models using classification or regression.
- Prediction of endpoints: survival, genomics, response to therapy, or tumor micro-environment

**However, few studies reported predicting the site of recurrence for GBM, and they are often limited to the recurrence in the peritumoral brain tissues.**

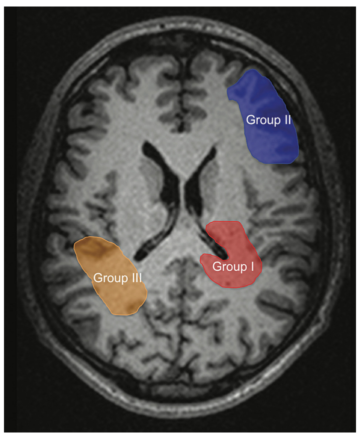
# The Role of Cancer Stem Cells in Glioblastoma



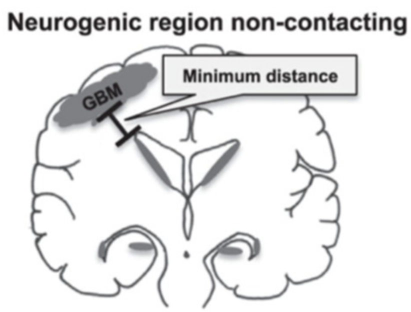

**Can we incorporate cancer stem cell theory into the image analysis for voxel-wise GBM recurrence prediction and RT intervention?**

# Radiation of the Stem Cell Niche

- Radiation, in theory, can decrease the number of brain tumor propagating cells in SVZ or SGZ to reduce the likelihood of recurrence or metastasis.
- However, studies in this field reported conflicting results, depending on RT doses and the size of the resection area.




[M Kimura et al., 2013]




[Linda Chen et al., 2015]

**Coarse characterization of stem cell niche involvement!**

**Need more quantitative metric!**

# Study 1

## Aim

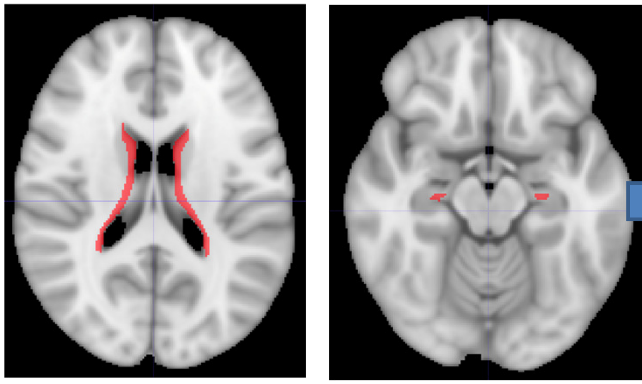
To develop a new inverse distance-based metric, proximity score (PS), to better characterize the geometric relationship of GBM tumors to stem cell niche zones.

## Data

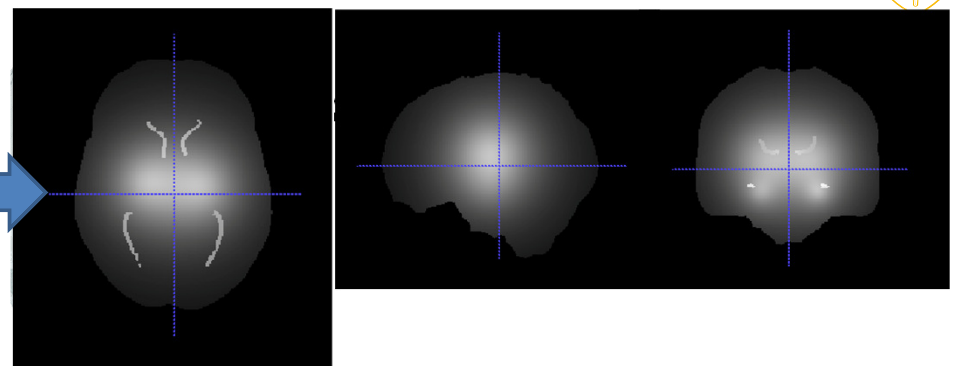
Two T1w MRI datasets were included in the study:

- 102 preoperative scans from the public TCIA dataset for prognostic stratification.
- 65 preoperative and follow-up scan pairs from two institutional databases for recurrent pattern identification.

# Our pipeline



SCN delineation

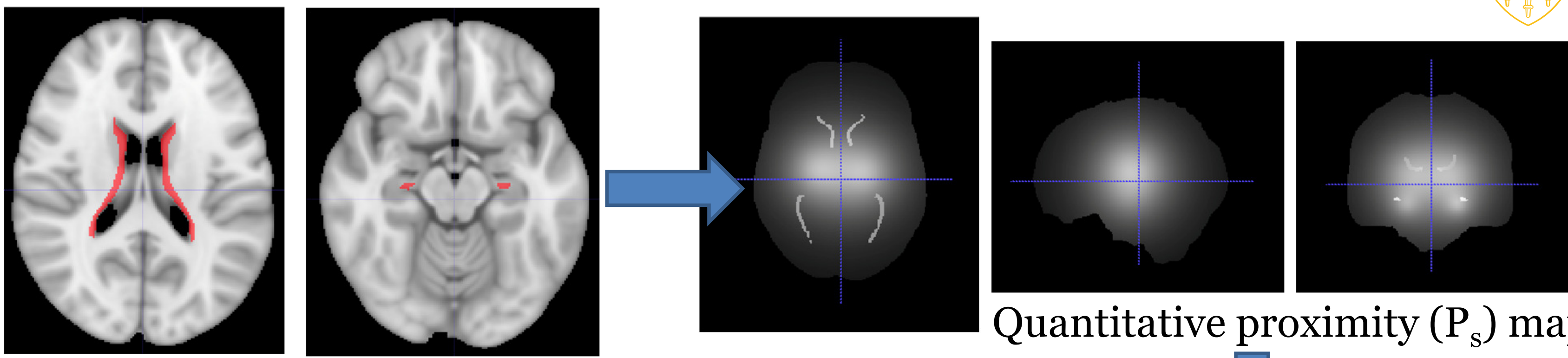


Quantitative proximity ($P_s$) map

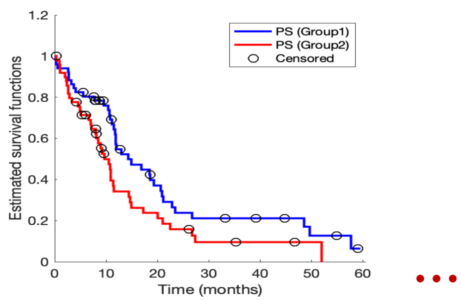
$$P_S(x) = \begin{cases} \frac{ID(x) - ID_{min}}{ID_{max} - ID_{min}}, if x \notin S \\ 1, if x \in S \end{cases}$$

$$ID(x) = \left(\sum_{i=1}^{N} \frac{1}{d(x, S_i)^p}\right)^{\frac{1}{p}}$$

# Our pipeline



Quantitative proximity ($P_s$) map




Statistical analysis

Deformable registration and mean $P_s$ score

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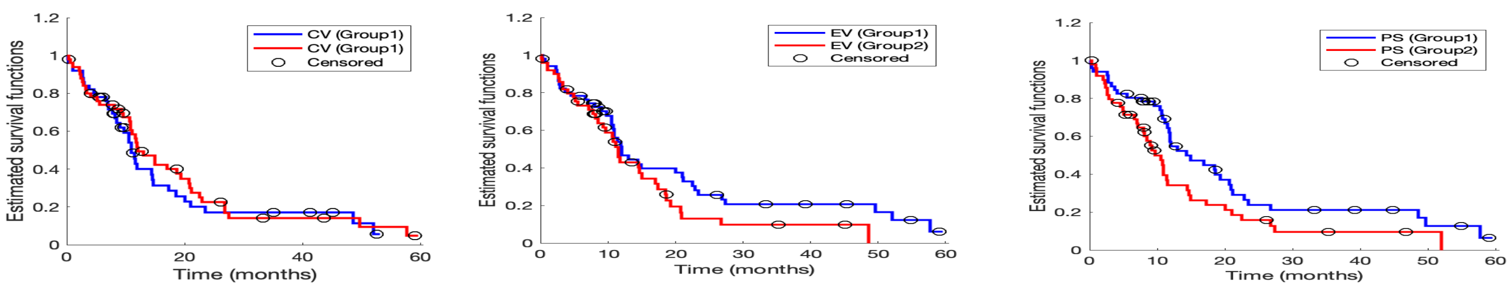
# Results (OS prediction and risk stratification)

- Among 3 SCN features, PS is the only significant predictor of OS (cox regression *p*-value = 0.0297)

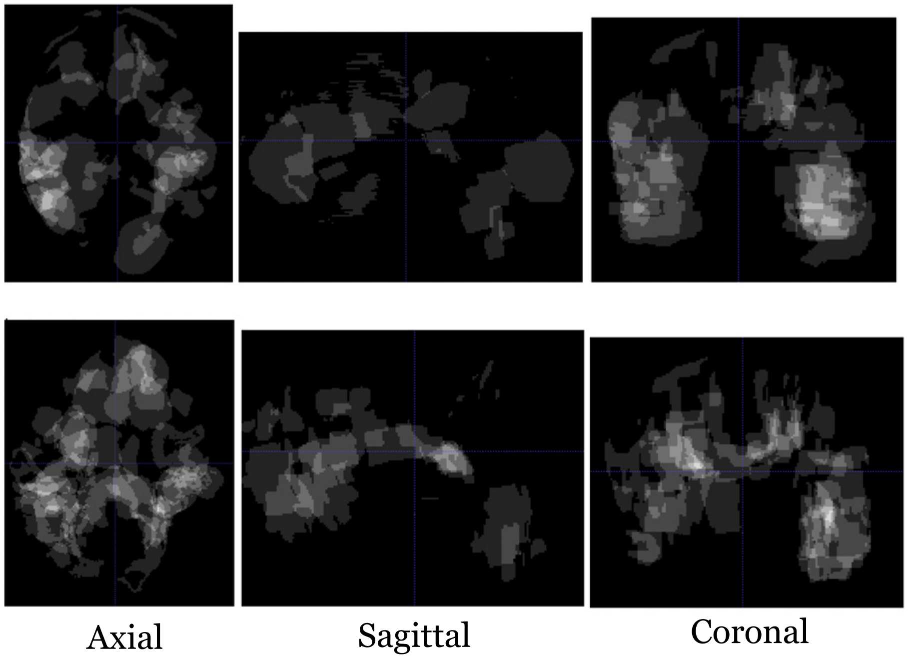
| | CV | EV | PS |
|---|---|---|---|
| HR | 0.9884 | 0.9676 | 4.45 |
| *p* | 0.5660 | 0.7483 | 0.0297 |

- PS is the best performer in risk stratification (log-rank $p$ = 0.0474).

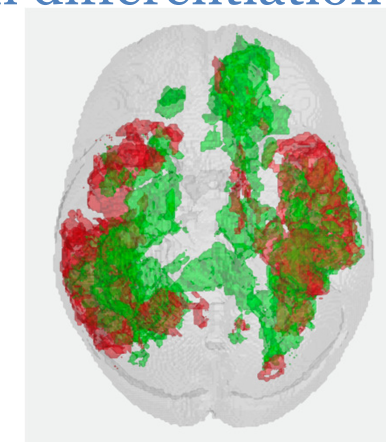



Kaplan-Meier plots of overall survival for groups of patients stratified by CV (log-rank p = 0.5829), EV (log-rank p = 0.1486), and PS (log-rank p = 0.0474). Censored observations are marked by black circles.

# Results (Primary vs. Recurrence pattern differentiation)

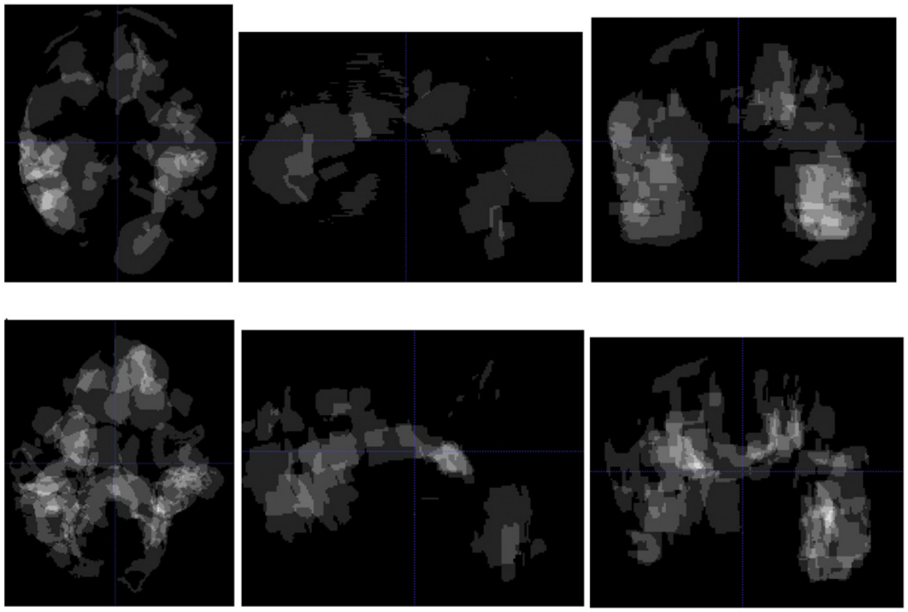



Illustrations of overlaid primary (upper row) and recurrent tumor (bottom row) locations from all the subjects.



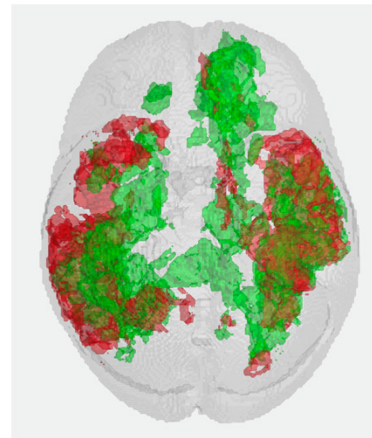
**Red: Original tumors**
**Green: Recurrence**

# Results (Primary vs. Recurrence)



Axial Sagittal Coronal

Illustrations of overlaid primary (upper row) and recurrent tumor (bottom row) locations from all the subjects.




| | Mean | SD | *p*-value |
|---|---|---|---|
| Original Tumor | 0.1994 | 0.1083 | 0.0017* |
| Recurrence | 0.2406 | 0.1162 | |

Group comparison of PS between primary and recurrent tumors. ($p = 0.0101$ for CV and $p = 0.0051$ for EV.)

# Summary of study 1

- Based on T1 MRI, a novel proximity score metric was developed to quantify tumor proximity to all SCN zones.
- Proximity score-based metrics outperformed traditional edge or center distance-based measurements in survival risk stratification.
- Proximity score best differentiated variations between primary and recurrent tumors in SCN proximities.

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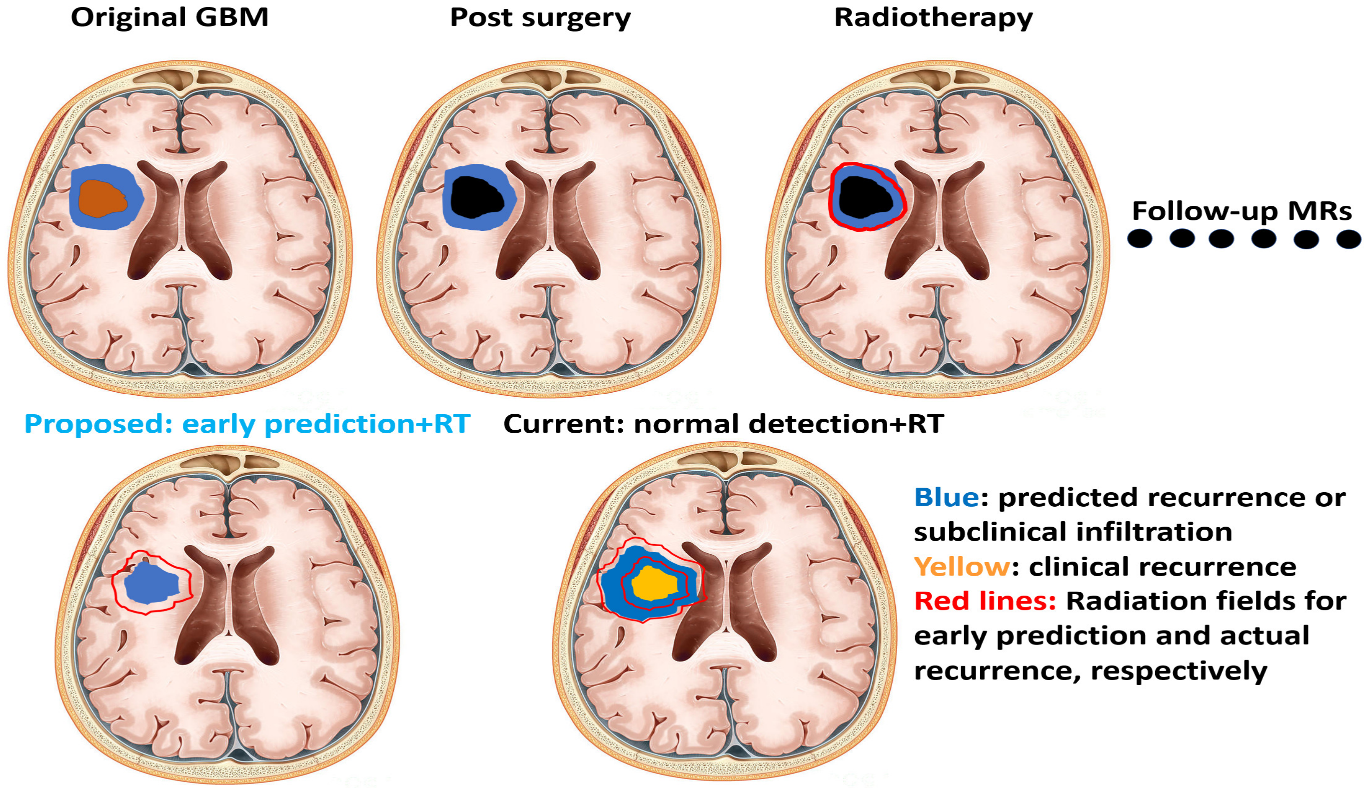
*Quantitative characterization of tumor proximity to stem cell niches: implications on recurrence and survival in GBM patients. 2021 PMID: 33600888*

# Study 2

## Advanced prediction of GBM recurrence (**TIME**) for personalized radiotherapy

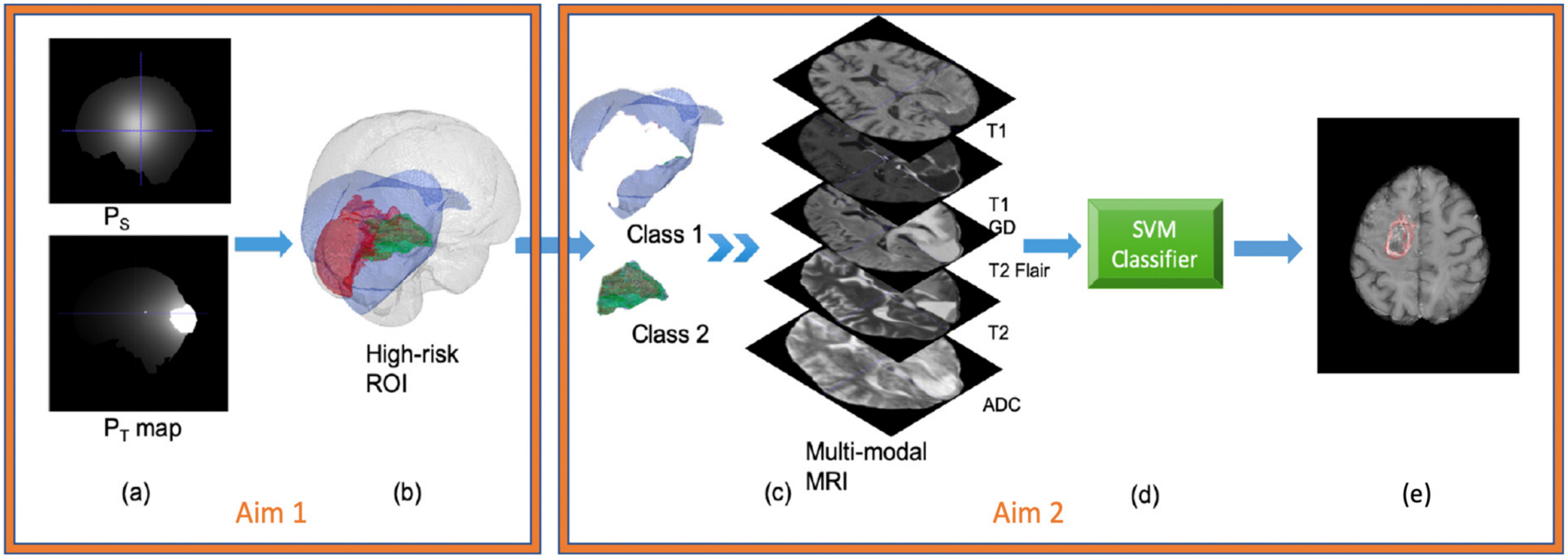
- Develop voxel-wise GBM recurrence prediction using multi-dimensional support vector machine (SVM) coupling with primary tumor and SCN proximity estimation.
- Demonstrate the radiation dose escalation can be achieved for early predicted recurrence.

# Motivation to treat subclinical infiltration early




**Blue**: predicted recurrence or subclinical infiltration
**Yellow**: clinical recurrence
**Red lines:** Radiation fields for early prediction and actual recurrence, respectively

# Our pipeline: overview

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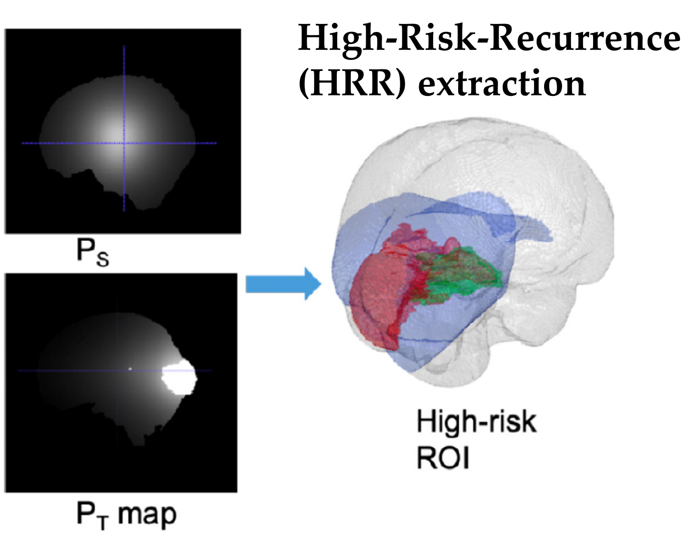
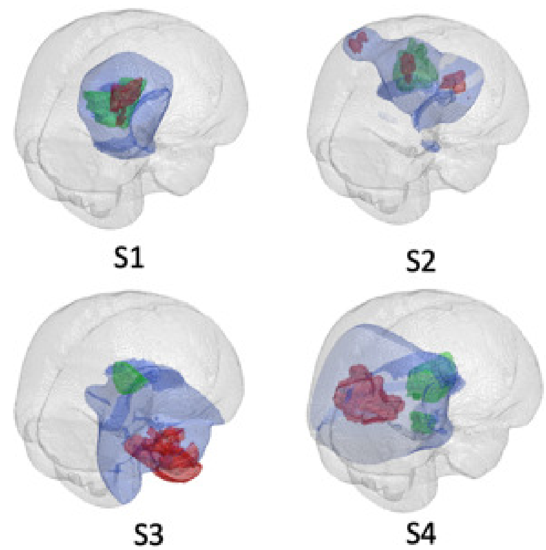
# Our pipeline: High Risk of Recurrence (HRR) estimation




**Red: Original tumors**
**Green: Recurrence**
**Blue: High Risk of Recurrence**

Four patient examples

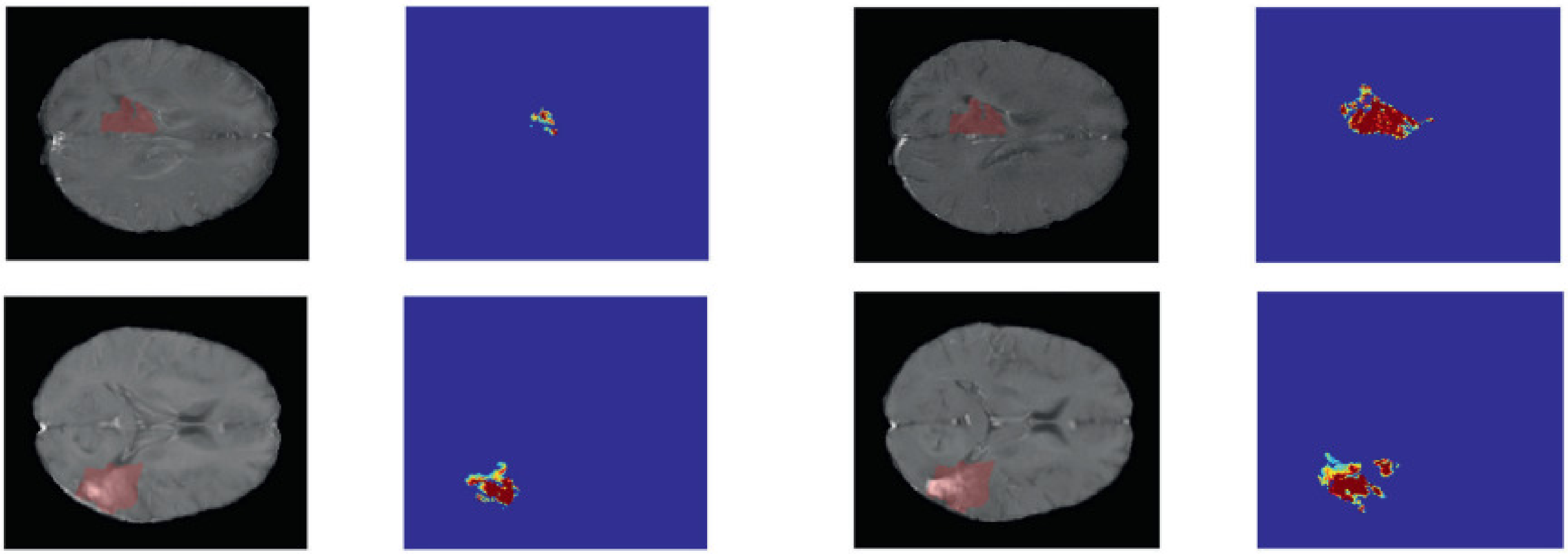
| | Training† | | Testing | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P* values |
| Recall | 0.81 | 0.13 | 0.80 | 0.10 | .591 |
| Precision | 0.68 | 0.14 | 0.69 | 0.14 | .684 |
| F1 | 0.73 | 0.12 | 0.73 | 0.10 | .978 |
| ABD (mm) | 8.14 | 6.33 | 7.49 | 6.19 | .722 |

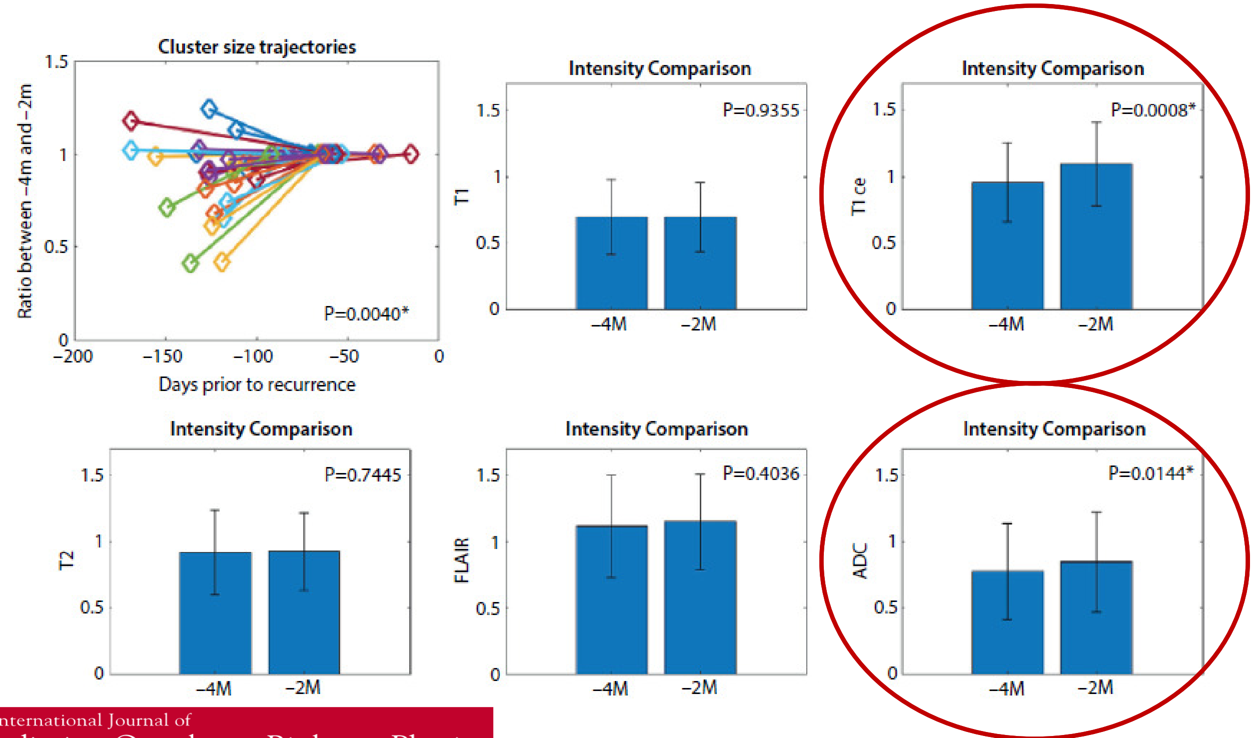
*Abbreviations:* ABD = average boundary distance; $SVM_{PE}$ = proximity estimation–based support vector machine.

[*] For both the training and testing data sets, 4 metrics (recall, precision, F1 score, and ABD) are presented, along with their corresponding groupwise comparison *P* values. No statistically significant ($P < .05$) differences were detected on the 4 metrics between the discovery and testing sets.

[†] For the training data set, performance scores are reported after 10-fold cross-validation.

# - 4 months - 2 months



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*Voxel-wise Prediction of Recurrent High-Grade Glioma via Proximity Estimation-Coupled Multidimensional Support Vector Machine, 2022, PMID: 34963559*

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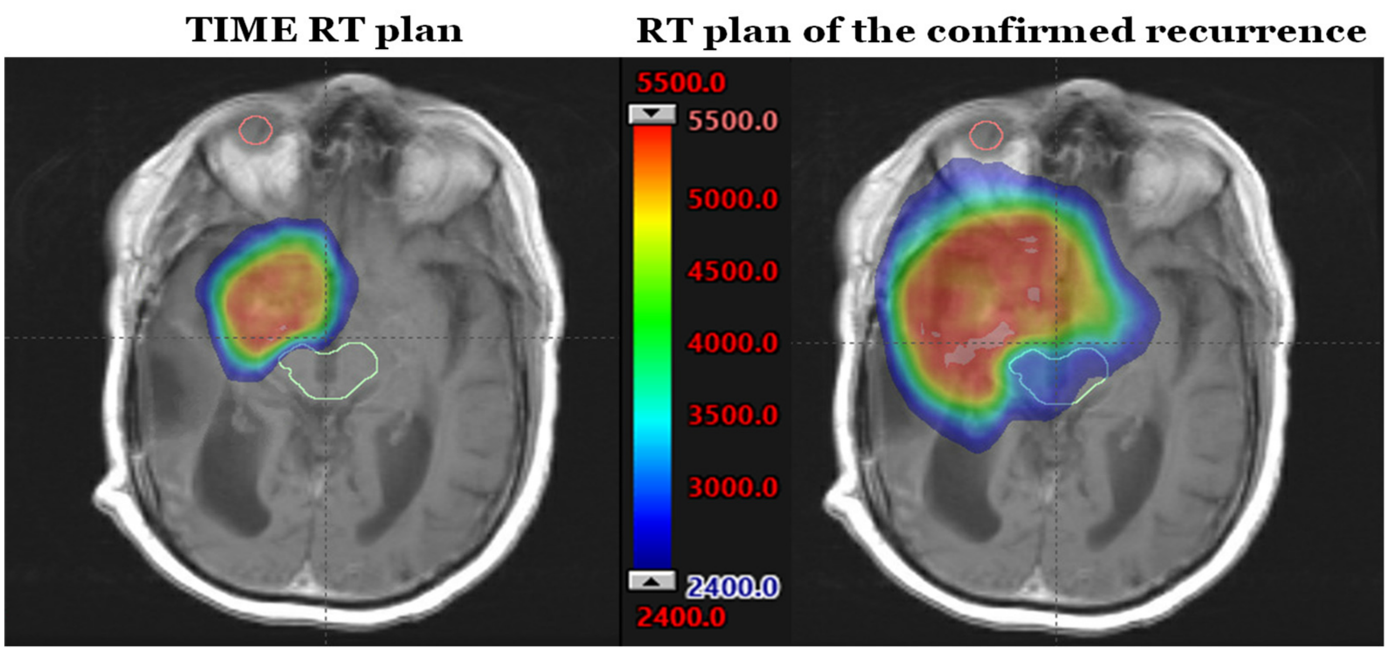
# Proposed early intervention



## Conclusion

- Tumor stem cell theory was quantitatively incorporated into MR image-based GBM recurrence prediction using proximity maps
- Both local and distant recurrences could be predicted at voxel level
- Virtual dose escalation on predicted clinical target volume shows significantly lower normal tissue doses while achieving higher tumor dose, compared with standard salvage RT
- The **TIME** model provides an advanced prediction tool to support subsequent early radiation interventional trial

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