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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R01 EB029088
R21 CA267139
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

Glioblastomas are genetic and transcriptional heterogeneous tumors. To improve clinical outcome, it's important to identify the cells of origin. The cancer stem cell theory hypothesized that neural stem cells could transform into brain tumor propagating cells, which could migrate into other brain regions and form a tumor.

There are two major neural stem cell niches in adult brain: subventricular zone (SVZ) and subgranular zone (SGZ).

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.

Coarse characterization of stem cell niche involvement!

Need more quantitative metric!

[M Kimura et al., 2013]

[Linda Chen et al., 2015]
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

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

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

Quantitative proximity ($P_s$) map

Statistical analysis

Deformable registration and mean $P_s$ score
Results (OS prediction and risk stratification)

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

<table>
<thead>
<tr>
<th></th>
<th>CV</th>
<th>EV</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.9884</td>
<td>0.9676</td>
<td>4.45</td>
</tr>
<tr>
<td>$p$</td>
<td>0.5660</td>
<td>0.7483</td>
<td>0.0297</td>
</tr>
</tbody>
</table>

- 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)

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Tumor</td>
<td>0.1994</td>
<td>0.1083</td>
<td>0.0017*</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0.2406</td>
<td>0.1162</td>
<td></td>
</tr>
</tbody>
</table>

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.

*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

Original GBM  Post surgery  Radiotherapy

Follow-up MRs

Proposed: early prediction+RT  Current: normal detection+RT

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

Keck Medicine of USC
Department of Radiation Oncology
Medical Physics
Our pipeline: overview
Our pipeline: High Risk of Recurrence (HRR) estimation

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

Four patient examples
<table>
<thead>
<tr>
<th></th>
<th>Training Mean</th>
<th>SD</th>
<th>Testing Mean</th>
<th>SD</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall</td>
<td>0.81</td>
<td>0.13</td>
<td>0.80</td>
<td>0.10</td>
<td>.591</td>
</tr>
<tr>
<td>Precision</td>
<td>0.68</td>
<td>0.14</td>
<td>0.69</td>
<td>0.14</td>
<td>.684</td>
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<tr>
<td>F1</td>
<td>0.73</td>
<td>0.12</td>
<td>0.73</td>
<td>0.10</td>
<td>.978</td>
</tr>
<tr>
<td>ABD (mm)</td>
<td>8.14</td>
<td>6.33</td>
<td>7.49</td>
<td>6.19</td>
<td>.722</td>
</tr>
</tbody>
</table>

*Abbreviations:* ABD = average boundary distance; $\text{SVM}_{PE}$ = 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
Voxel-wise Prediction of Recurrent High-Grade Glioma via Proximity Estimation-Coupled Multidimensional Support Vector Machine, 2022, PMID: 34963559
Proposed early intervention

TIME RT plan

RT plan of the confirmed recurrence
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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