Predicting spatial patterns of recurrence for glioblastoma using multi-parametric MRI classification

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Purpose Current prognoses for patients diagnosed with glioblastoma are grim, with only 2% of patients surviving three years [1]. Even after surgery, radiotherapy, and chemotherapy, in almost all cases tumors recur. Our aim is to provide a spatial map of predicted tumor recurrence prior to resection and therapy, in order to guide radiotherapy planning to improve survival and/or quality of life. Previous work in this area has focused on prediction of incidence of tumor recurrence [2], classification of tumor type and grade [3], segmentation of tumor tissues [4], and distinguishing treatment-related necrosis vs. recurrence [5]. To our knowledge, with one exception ([4], which included a small section with a prototype using just three subjects), this is the first work on prediction of location of tumor recurrence, using advanced image analysis and machine learning tools on multi-variate MRI.

Methods *Subjects:* Fourteen subjects with glioblastoma (WHO Grade IV) and subsequent recurrence, treated at our institution, were used. Potential subjects with a prior tumor or resection were excluded. *Image acquisition and processing:* Images acquired at pre-operative and post-operative time points include T1, T1 contrast enhanced (T1ce), T2, Flair, relative cerebral blood volume (rCBV), and diffusion tensor imaging, from which fractional anisotropy (FA), radial diffusivity (RAD), axial diffusivity (AX), and Trace (TR) were calculated. Intra-subject images were affinely registered within and across time points, and smoothing, inhomogeneity correction, skull stripping, and histogram matching were performed. *ROIs:* Two regions of interest (ROIs) were drawn for each subject: Recurring tissue, drawn under supervision of an expert, and non-recurring tissue (including healthy tissue far from tumor and abnormal-appearing tissue close to tumor). Using the affinely registered images, landmarks, and intermediate scans, a region was manually selected to indicate from where the recurrence originated. *Classification and probability maps:* A support vector machine (SVM) classification, libSVM, was trained for each voxel on recurring and non-recurring ROIs using 10 features (9 aforementioned images and time to recurrence in months, as described below). Leave-one-subject-out cross-validation produced recurrence probability maps for each subject. *Time to recurrence:* The number of months between pre-operative and post-recurrence images, ranging from 2 to 24 months, was used as an additional feature. For all recurring and non-recurring voxels in a given subject, the single value of time to recurrence was added as an additional feature. In addition to the known value, during testing the time-to-recurrence parameter was varied for each subject, producing a probability map for 2, 4, 6, 12, and 24 months.

Subj	AUC	Sens	Spec	Acc
1	0.91	41%	97%	97%
2	0.97	79%	96%	96%
3	0.72	21%	92%	92%
4	0.92	62%	92%	92%
5	0.73	0%	99%	99%
6	0.63	4%	97%	97%
7	0.98	20%	100%	100%
8	0.83	53%	93%	93%
9	0.20	0%	98%	98%
10	0.96	22%	100%	99%
11	0.86	3%	99%	99%
12	0.68	0%	100%	100%
13	0.68	0%	98%	98%
14	0.99	75%	99%	99%
Mean	0.79	27%	97%	97%
Std	0.21	29%	3%	3%

Table 1. Cross-validated statistics for each of 14 subjects. Abbreviations: Subject, area under the curve, sensitivity, specificity, accuracy, standard deviation.

Results Table 1 and Figure 1 show summary statistics and an example generated probability map, including progression over time.

Discussion As seen in Table 1, specificity of the algorithm is very high (mean 97%). Sensitivity is quite variable, from 0% to 79%. While specific cases show surprisingly good results, other cases may be difficult because recurrence progressed from tissue just adjacent to the manual ROI, or recurrence is distant and occurs in tissue which, in the pre-operative images, was identical to nearby tissue. Nevertheless, many of the 14 subjects have high AUC, and the ability of the algorithm to produce probability maps which in some cases capture recurrence progression in tissue which may be indistinguishable by human eye gives hope that these accuracies can continue to be improved.

The probability maps produced for various time points reveal in general (and specifically in Figure 1) that recurrence at earlier time points tends to be near the resection site, whereas recurrence at later time points tends to be farther away. This finding is consistent with current thinking that tissue nearer to the tumor contains more infiltrative tumor, which may recur more quickly. In this study, we have used the known value of time to recurrence to test the classifier; in practice, estimation of this parameter would be useful for selecting each subject's most relevant probability map within the time series. In general, we find that time to recurrence is an important parameter in capturing patterns of tumor progression.

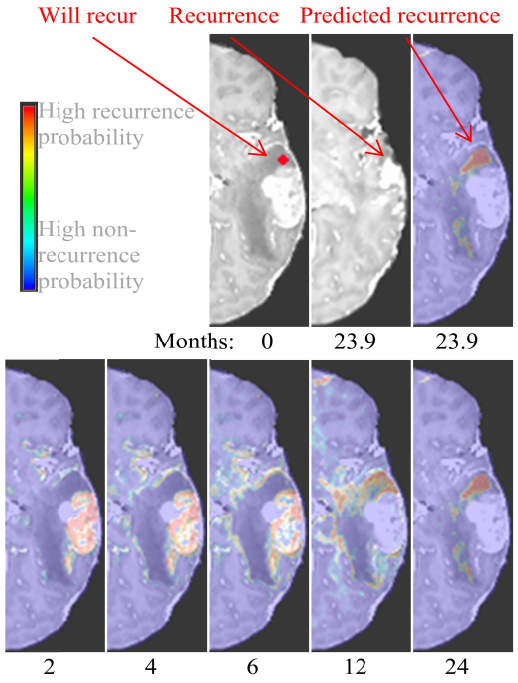

Figure 1. Predicted recurrence maps for subject 14 at different time points, cross-validated (model trained on subjects 1-13). Note that predictions in resected tissue (i.e. enhancing tissue) can be ignored, as those tissues are not in the post-recurrence time point. Top row: Pre-operative T1ce image at 0 months, with manually drawn red ROI indicating tissue which will recur; Post-recurrence T1ce image at 23.9 months, showing actual recurrence; Recurrence probability map generated for post-recurrence time point (23.9 months). Bottom row: Predicted recurrence maps at 2, 4, 6, 12, 24 months, overlaid on pre-operative T1ce image.

References

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Conclusion In this study, we have investigated a potential tool for prediction of location of recurrence of glioblastoma tumors. Using both conventional and non-conventional imaging modalities, time to recurrence, and SVM classification, we find that there is promise in these techniques, which may ultimately be used to guide radiation therapy dose distributions for longer survival and quality of life of brain tumor patients.