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Multi-parametric Analysis and Registration of Brain Tumors: Constructing Statistical Atlases and Diagnostic Tools of Predictive Value

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***Abstract*—We discuss computer-based image analysis algorithms of multi-parametric MRI of brain tumors, aiming to assist in early diagnosis of infiltrating brain tumors, and to construct statistical atlases summarizing population-based characteristics of brain tumors. These methods combine machine learning, deformable registration, multi-parametric segmentation, and biophysical modeling of brain tumors.**

I. Introduction

Infiltrative brain tumors, particularly relatively higher grade brain gliomas, have extremely poor prognosis, largely due to the fact that the tumor has typically infiltrated beyond the treated tumor mass, without necessarily significantly changing imaging characteristics that are conventionally used to flag the tumor. We present work towards multi-parametric analysis of brain glioma MR images, using an extensive imaging protocol including conventional imaging sequences, in addition to perfusion and DTI.

We evaluate three aspects of brain tumors: 1) multi-parametric voxel-wise imaging signatures that might potentially predict future tumor recurrence; 2) more global-scale imaging characteristics of the tumors, captured by multi-scale texture properties, which differentiate between different tumor types; 3) spatial location. Towards the last goal, we present deformable registration methods for constructing statistical atlases of tumor distribution, aiming to ultimately link spatial location and extent to outcome, potentially also involving radiation therapy dose distributions.

We now present these different components of our program.

II. Multi-parametric analysis and recurrence

In patients with brain tumors, clinicians and surgeons identify areas of the brain to resect. However, in the majority of patients, the brain tumor recurs. This study aims to find characteristic imaging patterns in tissue that is likely to recur, allowing surgeons to resect this tissue initially and presumably reduce the incidence of post-resection recurrence in brain tumors.

To accomplish this task, we have acquired multi-modal image data for 35 brain tumor patients with pre-operative and post-recurrence (also post-operative) time points and labeled tumor tissue types in many of these images. After processing this data for inter-subject comparison, we find the tissue in the pre-operative image that has recurred in the post-recurrence image by integrating structural MRI and DTI via pattern analysis methods [4]. Various deformable registration algorithms mapping the two time points are currently being tested. This pre-operative tissue which has post-operatively recurred is likely to contain subtle patterns visible using multi-modal imaging profiles (see Figure 1) and predictable using multi-modal high-dimensional pattern classification (in progress).

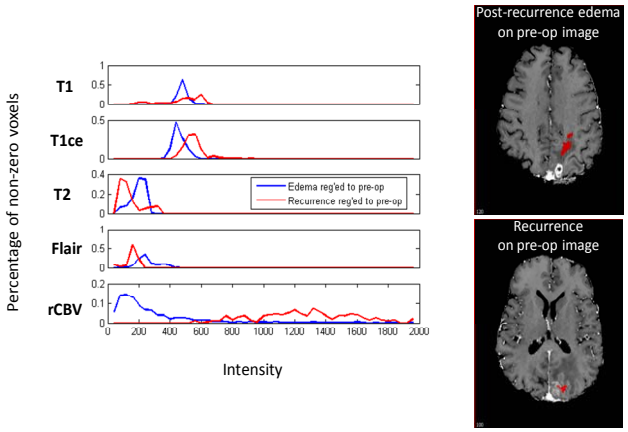

Figure 1. Image intensity differences between pre-operative tissues likely to recur (red) or not recur (blue).

III. Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme

The objective of this study is to provide an automated tool that may assist in the imaging evaluation of brain neoplasms by determining the glioma grade and differentiating between different tissue types, such as primary neoplasms (gliomas) from secondary neoplasms (metastases), as illustrated in Figure 2 [5].

The methodological framework consists of four parts: ROI definition, feature extraction, feature selection and classification based on Support Vector Machines (SVMs). We first reduce the number of features by eliminating the less relevant features using a forward selection method based on a ranking criterion, such as a two-tailed t-test, and then apply backward feature elimination using a feature subset selection method, such as the support vector machine recursive feature elimination (SVM-RFE) algorithm. For the purpose of comparison, we also investigated the performance of the simple t-test and the constrained Linear Discriminant Analysis (CLDA) algorithm [6]. CLDA maximizes the discriminant capability between classes

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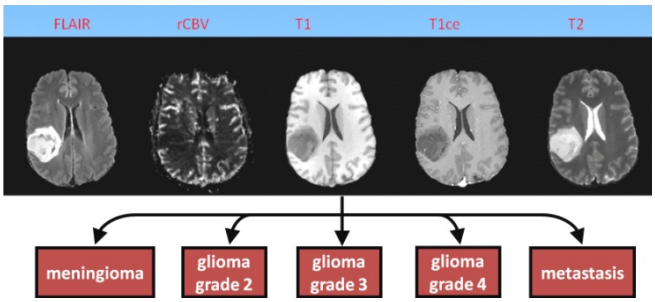

Figure 2. Brain tumor classification based on multi-parametric MRI.

without transforming the original features, as done by traditional LDA or PCA (Principle Component Analysis). Classification was performed by starting with the more discriminative features and gradually adding less discriminative features, until classification performance no longer improved. Three pattern classification methods were investigated for comparison: Linear Discriminant Analysis (LDA) with Fisher's Discriminant Rule [7], k-Nearest Neighbor (k-NN), and nonlinear SVMs [8].

The method was applied on a population of 102 brain tumors histologically diagnosed as metastasis (24), meningiomas (4), gliomas WHO grade 2 (22), gliomas WHO grade 3 (18), and glioblastomas (34). The classification accuracy (Acc) and the number of retained features (N_F) for the investigated algorithms are shown in Table 1 for the 10 pairwise problems. Moreover, the SVM classification accuracy, sensitivity, and specificity, assessed by leave-one-out cross-validation, were respectively 85%, 87%, and 79% for discrimination of metastases from gliomas, and 88%, 85%, and 96% for discrimination of high grade (grade III and IV) from low grade (grade II) neoplasms. Multi-class classification was also performed via a one-versus-all voting scheme. In this case the highest classification accuracy was achieved for metastasis (91.7%) and low grade glioma (90.9%), whereas the classification accuracy for GBM is reduced (29.4% are classified as grade III and 29.4% as metastasis).

IV. Predicting Survival of Patients with High Grade Gliomas Using a Data Mining Approach

A computer-assisted classification scheme combining conventional MRI, perfusion MRI and DTI was developed and used for predicting survival of patients with high-grade gliomas. Data analysis was performed in several stages. First the data were preprocessed and ROIs were semi-automatically segmented. Then, ROI-based analysis was performed to extract imaging characteristics from rCBV and DTI. The imaging characteristics were combined with clinical findings and tumor pathology descriptors obtained by visual inspection of conventional MR imaging in order to retrieve a complete set of diagnostic variables describing the pathology. Subsequently, due to the substantial number of variables, data mining procedures were utilized to discern relevant patterns of relationships within the dataset and eliminate irrelevant variables. At last, once a final set of relationships between variables were found, the datasets were classified using a decision tree algorithm.

Sixty-seven patients with high grade gliomas (17 anaplastic gliomas WHO grade III/IV and 50 glioblastomas multiforme or gliosarcomas WHO grade IV/IV) who underwent preoperative conventional and advanced MR imaging (perfusion, DTI) were examined. Survival was evaluated from baseline to death or, for cases which were not followed until death (e.g. living patients) from baseline to time of last available follow-up. A time threshold of 18 months was defined to differentiate the patients in two groups, with short or long-term survival. The relationship of survival to 55 variables was analyzed in a multivariate fashion by using data mining techniques. The variables included clinical parameters (age, gender), categorical or continuous tumor descriptors (anatomical and functional location of tumor, extent of resection, multifocality, edema, presence of cyst or necrosis, enhancement pattern), volume of enhancing and non-enhancing neoplastic tissue, and ROI-based imaging characteristics (mean, min, max, variance, peak of histogram)

Variable selection used a wrapper [10] to define the predictive value of each subset of attributes and the *Scatter Search* algorithm [11] to determine the search over the attributes. It identified as the overall most important variables the extent of resection, mass effect, volume of enhancing tissue, maximum B0 intensity and mean Trace intensity in the non-enhancing region (including edema or necrosis). These variables were used to construct a prediction model based on a J48 classification tree. The average classification accuracy, assessed by cross-validation, was 85.1%. Finally, we compared the predictive ability of histopathology (tumor) grade with the power of the constructed classification model through Kaplan-Meier survival curves. When tumors were classified according to histopathology (grade 3 versus grade 4), the survival of patients was not significantly different ($p = 0.17$), whereas class distinctions according to the prediction model were significantly associated with survival outcome ($p = 1.6E-07$). Thus, the prediction model classified malignant gliomas in a manner that better correlates with clinical outcome than standard histopathology.

V. Integrated Segmentation, Registration and Tumor Growth Modeling in Brain Glioma Patients

In this section, we propose an approach for joint segmentation and deformable registration of brain scans of glioma patients to a normal atlas, a key step in constructing statistical atlases from brain tumor patient images. This registration task is generally very challenging as there is no correspondence for the pathology in the healthy scans [12].

In addition, the healthy tissue in the brain scan is often severely deformed by the mass-effect of the tumor so that its shape is very different from that in the healthy brain scan. We address this issue by developing a new approach for brain tumor registration that explicitly models the mass effect of the pathology. The proposed method is based on

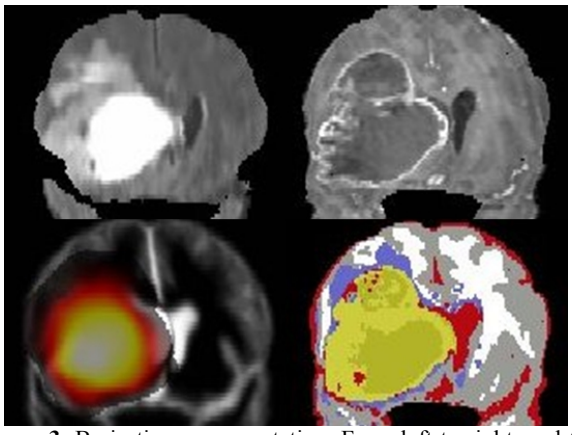

Figure 3. Brain tissue segmentation. From left to right, and top to bottom: FLAIR, T1 contrast enhanced, estimated tumor density, estimated segmentation.

the Expectation Maximization (EM) algorithm that incorporates diffusion-reaction to model the glioma growth for atlas seeding [13], a process which modifies the normal atlas into one with a tumor and edema. The modified atlas is registered into the patient space and utilized for the posterior probability estimation of various tissue labels. EM iteratively refines the estimates of the registration parameters, the posterior probabilities of tissue labels and the tumor growth model parameters.

We have applied this approach to 10 glioma scans acquired with four MR sequences (T1, T1contrast enhanced, T2 and FLAIR) and validated the result by comparing them to manual segmentations by clinical experts. A representative example is shown in Fig. 3.

VI. SUMMARY

We presented computer-based algorithms for analysis multi-parametric brain tumor images, aiming to construct diagnostic and prognostic tools. Multi-parametric signal properties of brain gliomas were examined using image analysis and machine learning techniques, and showed promise in terms of early identification of tissue that is likely to recur after resection. If this work is replicated to larger samples, it will point to new treatment procedures, including more aggressive resection and radiation therapy. Global tumor characteristics were used in machine learning tools to provide differential diagnosis of brain tumors, and to predict patient survival time. Finally, deformable registration methods now make it possible to construct statistical atlases from large numbers of patients, thereby allowing us to understand statistical trends across populations, using techniques that in other neuroimaging fields, particularly in neurological and neuropsychiatric disorders, have been found to be very informative.

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Table 1. Pairwise classification accuracy (Acc) obtained by leave-one-out cross-validation using different classifiers (LDA, kNN, SVM) and feature ranking methods (t-test with bagging, CLDA, SVM-RFE). MEN: meningioma, MET: metastasis, GL2, GL3 and GL4: glioma of grade II, III, and IV respectively.

classifier	**LDA**				**k-NN (k=3)**				**SVM**					
feature ranking	**t-test**		**CLDA**		**t-test**		**CLDA**		**t-test**		**CLDA**		**SVM-RFE**	
	N_F	*Acc*	N_F	*Acc*	N_F	*Acc*	N_F	*Acc*	N_F	*Acc*	N_F	*Acc*	N_F	*Acc*
met-men	12	92.9	27	85.7	11	96.4	32	89.3	5	96.4	1	85.7	**6**	**96.4**
met-gl2	79	95.7	8	84.8	2	97.8	55	97.8	2	97.8	3	95.7	**17**	**97.8**
met-gl3	1	81.0	12	83.3	70	90.5	152	88.1	8	88.1	10	88.1	**13**	**88.1**
met-gl4	2	58.6	95	77.6	9	74.1	16	79.3	91	84.5	150	89.7	**11**	**81.0**
men-gl2	1	100	1	100	1	96.2	2	96.2	1	96.2	12	96.2	**9**	**96.2**
men-gl3	3	81.8	5	95.5	15	95.5	2	90.9	9	86.4	4	90.9	**15**	**90.9**
men-gl4	4	86.8	11	100	12	97.4	4	97.4	10	97.4	36	94.7	**1**	**97.4**
gl2-gl3	74	70.0	101	77.5	9	67.5	1	72.5	51	72.5	1	75.0	**43**	**75.0**
gl2-gl4	11	76.8	19	78.6	33	98.2	38	98.2	18	98.2	12	98.2	**7**	**96.4**
gl3-gl4	5	67.3	35	69.2	154	84.6	141	84.6	104	94.2	78	92.3	**76**	**90.4**