

Improving Prediction on Overall Survival of Patient with Brain Tumor

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Abstract—The paper proposes to improve prediction on the life expectancy of patients suffering from High-Grade Glioma tumor. Automated brain tumor segmentation is obtained from the Magnetic Resonance Image using the existing Convolutional Neural Network. The segmentation is made robust by preprocessing the images with bias field correction followed by normalization. Then SVM classifier is pre-trained on features extracted from ground truth data and tested on features extracted from the CNN segmented images. The proposed implementation uses a smaller set of features and achieves higher accuracy for prediction of patient overall survival when compared to state-of-the-art methods.

Index Terms—Brain Tumor Segmentation, Convolutional Neural Networks (CNN), MRI, Overall Survival (OS), Support Vector Machine (SVM)

I. INTRODUCTION

The medical fraternity considers brain tumor amongst most fatal type of cancer [1], [2]. Cancers are divided into two categories based on origin and malignancy. Former is further classified as primary and secondary. The primary tumor develops in the brain whereas secondary spreads from another body part to the brain. According to the World Health Organization (WHO), malignancy based tumors can be classified in grades I to IV according to its increasing aggressiveness [3], [5].

High-Grade Glioma (HGG) which are considered to be grade III and grade IV tumor, needs immediate action in terms of treatment as it becomes malignant and grows at faster rate [3], [6]. It may lead to patient's death in less than two years, whereas Low-Grade Glioma (LGG) is considered to be the benign tumor which is slow growing and the patient has several years of life expectancy.

Magnetic Resonance Imaging (MRI) is a preferred technique for capturing tumors in brain [2]. It is non-invasive, does not use harmful X-rays, and also provides good soft tissue contrast [7]. Usually, MRI sequences are acquired by supplying complementary information [4]. Once MR images are captured, human expert scans them for the tumor diagnosis. This task is quite challenging, needs expertise

and the time taken due to the large volume of the data is a concern [8]. This motivates the need for automated or semi-automated brain tumor segmentation.

Methods for automated brain tumor segmentation are divided into three categories: basic, generative, and discriminative methods [14]. With the growth of deep learning most state-of-the-art methods use Convolutional Neural Network(CNN) for pixel-wise classification [1]. Similarly, a Fully Convolutional Network (FCN) focuses on semantic segmentation and segments entire tumor from an MRI image [9].

Many methods further segment and label tumor into its constituent parts. The tumor can be classified into substructures like necrosis, enhancing tumor and edema. Size of the tumor along with the size of these substructures plays the major role in treatment planning of the patient and predict the overall survival (OS). In [16], a U-net based model for tumor segmentation and radiomic based features were used for overall survival prediction. The tumor was characterized by image-based features computed from the segmentation masks. These features are then used to train a Random Forest Regressor (RFR) with 1000 trees and ensemble of small multilayer perceptrons (MLP) to complement the output of the regression forest for survival prediction. They obtained accuracy of 52.6% for overall survival and the Spearman correlation coefficient of 0.496.

In another attempt at survival prediction [17], the authors used pre-trained AlexNet to segment the brain tumor. The features from these segments are used to train the Linear Discriminant for survival prediction. The texture features resulted in the accuracy of 46%, and Histogram features achieved an accuracy of 68.5%. The authors developed a fully automated model for auto-segmentation of the Glioma brain tumors in multimodal MRIs [18]. The prediction of patient overall survival was based on SVM learning algorithms. They reported 100% accuracy for overall survival prediction on a set of 16 test samples. In [19], an FCNN architecture was used for tumor segmentation and the extracted features were fed to SVM classifier for OS prediction. A preprocessing step on MR scans is done using Z-score normalization to overcome multi-center data and magnetic field inhomogeneities. Also,

post-processing is implemented using connected components to remove components below a threshold. The features are extracted from segmented regions and fed to SVM with a linear kernel. The reported accuracy for OS prediction is 60%.

In this paper, we propose a model for prediction of patients overall survival using the BraTS 2017 [9], [11] dataset. We have analyzed the correlation of various feature vectors with patient's overall survival and shown the significance of 'Age' and 'Amount of Edema' features on OS. The MRI hyper-cubes are preprocessed for bias field correction and normalization. Then MRI images are segmented using existing state-of-the-art CNN. The extracted features are used to train SVM with RBF kernel. The SVM achieves accuracy of 82% for patient OS prediction which is better than existing state-of-the-art methods.

This paper is organized as follows. Section II presents preliminaries about the BraTS dataset used in the proposed work. Section III covers the CNN used for brain tumor segmentation and also the SVM for overall survival prediction. Section IV discusses the experimental results. Finally, Section V concludes the paper, with suggestions to further improve the OS prediction.

II. MULTIMODAL BRAIN TUMOR SEGMENTATION CHALLENGE

The multimodal brain tumor segmentation (BraTS) challenge invites researchers to develop robust brain tumor segmentation techniques from magnetic resonance imaging scans [9], [11]. In order to pinpoint the clinical relevance of segmentation task, the BraTS 2017 challenge also focused on the prediction of patient overall survival. The BraTS 2017 challenge comprised of two tasks: segmentation of the Gliomas, and prediction of patient overall survival. The dataset [9], [11]–[13] comprised of clinically-acquired 3T multimodal MRI scans and all the ground truth labels were manually revised by expert board certified Neuro Radiologists. Annotations comprise the GD-enhancing tumor (ET - label 4), the peritumoral edema (ED - label 2), and the necrotic and non-enhancing tumor (NCR/NET - label 1), as described in the [9]. The dataset was distributed after pre-processing, i.e., co-registered to the same anatomical template, interpolated to the same resolution ($1mm^3$) and skull-stripping [10]. The dataset had 210 HGG samples and 75 LGG samples, with each sample having four MRI modalities (T_1 , T_2 , T_1C and FLAIR) along with the ground truth. Each sample has 155 slices with 240x240 pixels per slice. Also, the overall survival, defined in days, is included in a comma-separated value (.csv) file with 'Patient ID', 'Age' for 163 samples. The suggested classes for classification based on the prediction of OS were long-survivors (e.g., >15 months), short-survivors (e.g., <10 months), and mid-survivors (e.g. between 10 to 15 months).

III. SYSTEM MODEL

We use two-fold segmentation and classification for brain tumor segmentation and patient overall survival prediction. An 11-layer CNN model [1] is used for the segmentation of HGG tumor after applying pre-processing steps. The segmentation results thus obtained are used as input features for the pre-trained SVM. The model classifies overall patient survival into three classes: Class 0 (short-term survivor), Class 1 (mid-term survivor), or Class 2 (long-term survivor).

The 210 HGG samples are further divided into 159 training and 51 validation samples. The overall survival data for 51 test samples were available and they are balanced across three classes i.e., 0, 1, and 2 with 17 samples per class.

A. CNN Model for Segmentation

Reimplementation of CNN model in [1] is done for tumor segmentation. The architecture is robust and had performed very well in BRATS 2015 challenge. The authors [1] proposed separate CNN models for HGG and LGG. In this paper, we have used the HGG based model due to the availability of the OS for 163 HGG patients in BraTS 2017 dataset. The HGG CNN architecture has 11-layers as shown in Fig. 1. The segmentation is improved by carrying out additional pre-processing steps of bias field correction [15] followed by normalization with zero mean and unit variance.

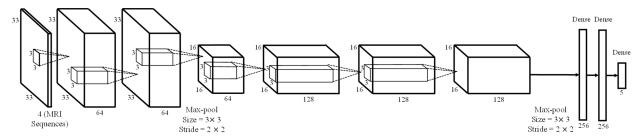


Fig. 1: CNN architecture for HGG [1].

B. SVM Model for Classification based on Patient OS

The segmented output from CNN is used to compute the feature vectors which are then fed to the Support Vector Machine. It carries out the classification of the samples based on the patient overall survival. We use the ground truth labels available with the images of the BraTS 2017 [12], [13] to derive features for training the SVM. The four feature vectors as shown in Table I are extracted and they are mapped to the OS data as output labels. Subsequently, pixel count is obtained for each tumor class label: 1, 2, and 4, and stored in a file which is used as the input for training the SVM.

After saving the training database, the Radial Basis Function (RBF) kernel is used for training the SVM. The RBF kernel is more flexible than Linear and Polynomial kernels. It can model infinitely differentiable functions better than a polynomial kernel. The hyper-parameters (C and γ) for the kernel are tuned by grid-search over a range of values to get the highest accuracy for the dataset. The 51 test samples are segmented using the CNN. The features are extracted

TABLE I: Features for SVM training.

Feature	Detail
Age	Age of patient taken directly from the BRATS 2017 dataset
Amount of Necrotic	# of necrotic pixels / # of total tumor pixels
Amount of Edema	# of edema pixels / # of total tumor pixels
Amount of Enhancing tumor	# of enhancing tumor pixels / # of total tumor pixels
Amount of Tumor	# of tumor pixels/ # of brain pixels

from these segments and fed to the trained SVM model for the prediction of the OS.

IV. EXPERIMENTAL RESULTS

We have used NVIDIA Quadro K5200 and Quadro P5000 GPU for training and testing of CNN and the AMD A10-4655M AMU with *Radeon HD* graphics for the SVM classification. The software used are as follows: Python 2.7 and 3.5, Tensorflow, Keras, Nibabel, N4ITK for CNN based segmentation and Sklearn for SVM based prediction of the patient survival.

The CNN (without augmentation) trained over 159 HGG samples with 100,000 patches, took around 30 minutes to complete training. It took around 2 hours to train the samples augmented with 90-degree rotation. The 51 HGG test samples took around 21 hours for segmentation and the results are shown in Fig. 2.

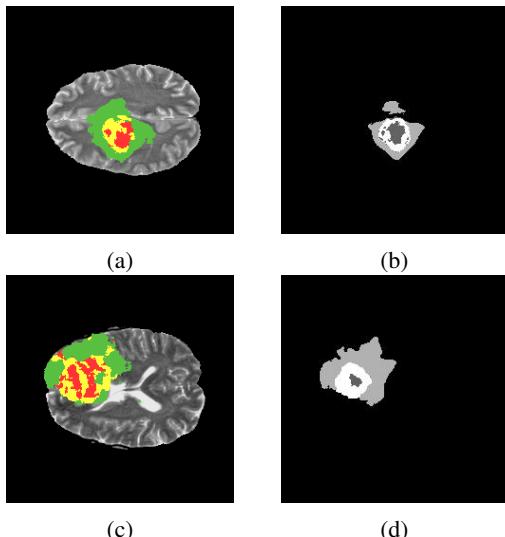


Fig. 2: Segmenration results: a) Patient-1 segmented result, b) Patient-1 Ground Truth, c) Patient-2 segmented result, and d) Patient-2 Ground Truth.

Extraction of features from ground truth labels of 163 HGG samples with OS data took around 1 hour. The SVM training

TABLE II: SVM results with Ground Truth test samples.

Class 0			Class 1			Class 2		
Actual Patients	Detected Patients	Acc.	Actual Patients	Detected Patients	Acc.	Actual Patients	Detected Patients	Acc.
17	17	100%	17	17	100%	17	17	100%

TABLE III: SVM results with CNN segmented test samples.

Class 0			Class 1			Class 2		
Actual Patients	Detected Patients	Acc.	Actual Patients	Detected Patients	Acc.	Actual Patients	Detected Patients	Acc.
17	13	76%	17	15	88%	17	14	82%

on RBF kernel (hyper-parameters: $C = 10$ and $\gamma = 10$) is completed within few seconds. The overall survival is then predicted by supplying features to SVM for classification. The classification results when ground truth data is used for testing SVM classifier is shown in Table II. The classifier accuracy when it is tested with CNN segmentation is shown in Table III. It shows that Class 1 has the highest accuracy of 88%. The overall accuracy as seen from the Table IV for Ground Truth test data is 100% and it is 82% with CNN segmentation.

Table V compares accuracy of the proposed method with other state-of-the-art techniques. Compared to [19], the proposed method has higher accuracy. Also it uses different SVM kernel (RBF) and requires lesser features for training. The method in [18] achieved 100% accuracy but it is over very small test samples (16), whereas, the proposed method is tested with higher number of samples (51).

A. Feature Analysis

We find the correlation between feature and overall survival to analyze the impact of the feature on survival prediction. The results are shown in the Table VI. We found an anomaly with respect to feature 'Amount of Edema'. The correlation came out to be positive, which means that the trend of the survival and this feature vector is in the same direction. This contradicts our understanding of the tumors where each subpart(feature) must have a negative correlation with OS i.e., the existence of an inverse relationship between feature and OS. Also, we note that the 'Age' has highest negative correlation compared to other features.

TABLE IV: Overall SVM accuracy.

	Correct Detection	Incorrect Detection	Overall Accuracy
Ground Truth	51	0	100%
CNN Segmentation	42	9	82%

TABLE V: Comparison with state-of-the-art methods.

Ref. and Features	Accuracy %
[16], Radiomic	52.6
[17], Texture	46
[17], Histogram	68.5
[18]	100
[19]	60
Proposed	82

TABLE VI: Correlation of Feature and overall survival data.

	Age	Amt. of Necrotic	Amt. of Edema	Amt. of Enhancing Tumor	Amt. of Tumor
Correlation	-0.372	-0.101	0.114	-0.084	-0.109

TABLE VII: Significance of 'Age' and 'Amount of Edema'.

	Correct Detection	Incorrect Detection	Overall Accuracy
Removing 'Age'	18	33	35%
Removing 'Amount of Edema'	44	7	86%

We train and test the SVM again by removing two feature vectors: 'Age' and 'Amount of Edema' one by one for further analysis. The results are summarized in Table VII. When 'Age' feature is removed, the classification results show a significant decrease in the accuracy. This means that 'Age' is the most important feature vector for prediction of the OS. Also, when feature 'Amount of Edema' is removed there is a marginal increase in the overall accuracy of OS prediction. On further research and discussions with Medical experts, it was found that 'Edema' is an inflammation or swelling and does not affect the overall survival of the patient. 'Edema' is an important factor in some cases where the tumor is near respiratory centers. The 'Necrosis' is the dead matter and has the highest impact on patient survival, whereas 'Enhancing Tumor' was part of the tumor which would soon be converted to a dead matter.

V. CONCLUSION

We have successfully developed an SVM model for prediction of patient overall survival. The CNN was trained on BraTS 2017 dataset and the segmentation results with labels were produced. Further, we combine these labels with the patient age and use them as feature vectors for prediction of patient overall survival. The SVM used for OS prediction was trained using ground truth labels from BraTS 2017 OS dataset. The proposed method resulted into over all accuracy of 82% for OS prediction on CNN segmented label. We also analysed the correlation of the feature vectors and overall survival and found 'Age' to be the most important feature, followed by volume of necrosis and enhancing tumor.

The accuracy can be further enhanced by implementing post-processing with morphological operations. We also propose use of three more feature vectors as shown in Table VIII for improving the prediction accuracy.

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TABLE VIII: Proposed additional Features

Feature Vectors	Detail
Slices of Tumor with Necrotic	# of slices where Necrotic cells are present in the tumor
Slices of Tumor with Edema	# of slices where Edema cells are present in the tumor
Slices of Tumor with Enhancing Tumor	# of slices where Enhancing Tumor cells are present in the tumor

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REFERENCES

- [1] Pereira, S., Pinto, A., Alves, V. and Silva, C. (2016). Brain Tumor Segmentation Using Convolutional Neural Networks in MRI Images. IEEE Transactions on Medical Imaging, 35(5), pp.1240-1251.
- [2] DeAngelis, Lisa M. "Brain tumors." New England Journal of Medicine 344.2 (2001): 114-123.
- [3] Kleihues, Paul, Peter C. Burger, and Bernd W. Scheithauer. "The new WHO classification of brain tumours." Brain pathology 3.3 (1993): 255-268.
- [4] S. Bauer et al., "A survey of MRI-based medical image analysis for brain tumor studies," Phys. Med. Biol., vol. 58, no. 13, pp. 97129, 2013.
- [5] Ohgaki, Hiroko, and Paul Kleihues. "Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas." Journal of Neuropathology & Experimental Neurology 64.6 (2005): 479-489.
- [6] Louis, David N., ed. WHO classification of tumours of the central nervous system. Vol. 1. WHO Regional Office Europe, 2007.
- [7] Liang, Zhi-Pei, and Paul C. Lauterbur. Principles of magnetic resonance imaging: a signal processing perspective. SPIE Optical Engineering Press, 2000.
- [8] Bankman, Isaac, ed. Handbook of medical image processing and analysis. Elsevier, 2008.
- [9] Menze BH, Jakab A, Bauer S, Kalpathy-Cramer J, Farahani K, Kirby J, Burren Y, Porz N, Slotboom J, Wiest R, Lanczi L, Gerstner E, Weber MA, Arbel T, Avants BB, Ayache N, Buendia P, Collins DL, Cordier N, Corso JJ, Criminisi A, Das T, Delingette H, Demiralp , Durst CR, Dojat M, Doyle S, Festa J, Forbes F, Geremia E, Glocker B, Golland P, Guo X, Hamamci A, Iftekharuddin KM, Jena R, John NM, Konukoglu E, Lashkari D, Mariz JA, Meier R, Pereira S, Precup D, Price SJ, Raviv TR, Reza SM, Ryan M, Sarikaya D, Schwartz L, Shin HC, Shotton J, Silva CA, Sousa N, Subbanna NK, Szekely G, Taylor TJ, Thomas OM, Tustison NJ, Unal G, Vasseur F, Wintermark M, Ye DH, Zhao L, Zhao B, Zikic D, Prastawa M, Reyes M, Van Leemput K. "The Multimodal Brain Tumor Image Segmentation Benchmark (BRATS)", IEEE Transactions on Medical Imaging 34(10), 1993-2024 (2015) DOI: 10.1109/TMI.2014.2377694
- [10] Braintumorsegmentation.org. (2018). MICCAI BRATS - The Multi-modal Brain Tumor Segmentation Challenge. [online] Available at: <http://braintumorsegmentation.org/>.
- [11] Bakas S, Akbari H, Sotiras A, Bilello M, Rozycski M, Kirby JS, Freymann JB, Farahani K, Davatzikos C. "Advancing The Cancer Genome Atlas glioma MRI collections with expert segmentation labels and radiomic features", Nature Scientific Data, 4:170117 (2017) DOI: 10.1038/sdata.2017.117
- [12] Bakas S, Akbari H, Sotiras A, Bilello M, Rozycski M, Kirby J, Freymann J, Farahani K, Davatzikos C. "Segmentation Labels and Radiomic Features for the Pre-operative Scans of the TCGA-GBM collection", The Cancer Imaging Archive, 2017. DOI: 10.7937/K9/TCIA.2017.KLXWJJ1Q
- [13] Bakas S, Akbari H, Sotiras A, Bilello M, Rozycski M, Kirby J, Freymann J, Farahani K, Davatzikos C. "Segmentation Labels and Radiomic Features for the Pre-operative Scans of the

- TCGA-LGG collection”, The Cancer Imaging Archive, 2017. DOI: 10.7937/K9/TCIA.2017.GJQ7R0EF
- [14] Agrawat, Rupal R., and Mehul S. Raval. “Deep Learning for Automated Brain Tumor Segmentation in MRI Images.” Soft Computing Based Medical Image Analysis. 2018. 183-201.
 - [15] Tustison, Nicholas J., et al. “N4ITK: improved N3 bias correction.” IEEE transactions on medical imaging 29.6 (2010): 1310-1320.
 - [16] Isensee, Fabian, et al. “Brain Tumor Segmentation and Radiomics Survival Prediction: Contribution to the BRATS 2017 Challenge.” 2017 International MICCAI BraTS Challenge (2017).
 - [17] Chato, Lina, and Shahram Latifi. “Machine Learning and Deep Learning Techniques to Predict Overall Survival of Brain Tumor Patients using MRI Images.” Bioinformatics and Bioengineering (BIBE), 2017 IEEE 17th International Conference on. IEEE, 2017.
 - [18] Osman, Alexander FI. “Automated Brain Tumor Segmentation on Magnetic Resonance Images and Patient’s Overall Survival Prediction Using Support Vector Machines.” International MICCAI Brainlesion Workshop. Springer, Cham, 2017.
 - [19] Varghese Alex, Mohammed Safwan, and Ganapathy Krishnamurthi, Brain Tumor Segmentation from Multi Modal MR images using Fully Convolutional Neural Network, BRATS proceedings, MICCAI 2017.

APPENDIX A
LAYER-WISE DETAILS OF CNN ARCHITECTURE FOR HGG

Here, in Table IX we show layer by layer size parameters of the HGG architecture used in CNN implementation [1]. Also, design parameters are shown in Table X.

Layers	Type	Filter Size	Stride	Filters	FC Units	Input
Layer 1	Convolutional	3 x 3	1 x 1	64	-	4 x 33 x 33
Layer 2	Convolutional	3 x 3	1 x 1	64	-	64 x 33 x 33
Layer 3	Convolutional	3 x 3	1 x 1	64	-	64 x 33 x 33
Layer 4	Max Pool	3 x 3	2 x 2	-	-	64 x 33 x 33
Layer 5	Convolutional	3 x 3	1 x 1	128	-	64 x 16 x 16
Layer 6	Convolutional	3 x 3	1 x 1	128	-	128 x 16 x 16
Layer 7	Convolutional	3 x 3	1 x 1	128	-	128 x 16 x 16
Layer 8	Max Pool	3 x 3	2 x 2	-	-	128 x 16 x 16
Layer 9	FC	-	-	-	256	6272
Layer 10	FC	-	-	-	256	256
Layer 11	FC	-	-	-	5	256

TABLE IX: CNN Architecture for HGG [1].

Stage	Hyperparameters	Value
Initialization	bias	0.1
Initialization	weights	Xavier
Leaky ReLU	alpha	0.33
Dropout	p	0.1
Training	epochs	20
Training	batch	128

TABLE X: Design Parameters of CNN Architecture

APPENDIX B
CNN SEGMENTATION RESULTS

Some other results of Brain Tumor Segmentation from CNN HGG Architecture.

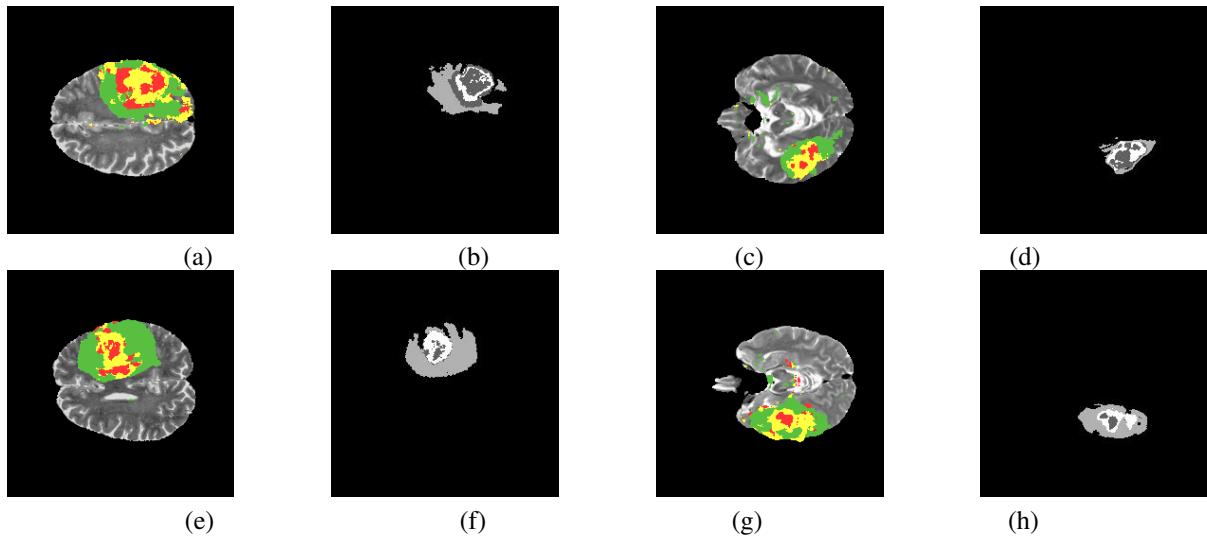


Fig. 3: CNN Segmentation results: a) Patient-1 segmented result, b) Patient-1 Ground Truth, c) Patient-2 segmented result, and d) Patient-2 Ground Truth, e) Patient-3 segmented result, f) Patient-3 Ground Truth, g) Patient-4 segmented result, and h) Patient-4 Ground Truth