

Predicting Overall Survival in Patients with Glioma

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August 2020

1 Abstract

Brain metastases are secondary tumors that grow in the brain and find their source in a cancer developed in some other part of the body[1]. Treatment often involves Stereotactic Radiosurgery (SRS) that reduces the chance of recurrence by 50% but leads to a complication called Necrosis. There is an inherent difficulty in differentiating tumor recurrence from necrosis and in turn predicting the overall survival of patients using Magnetic Resonance Imaging(MRI) sequences. Surgical resection is the most sought after solution but it exposes patients to significant morbidity. Thus, there is an unmet need for a non-invasive method to detect brain metastases recurrence and in turn predict the overall survival of patients with malignant tumors. Extracting and exploring features of the lesions and estimating the overall survival days will aid in disease progression monitoring and making treatment related decisions to alleviate pain. Owing to the ready availability of imaging and survival information of Glioma patients, in this exploratory project, we focus on using the MRI sequences of patients diagnosed with primary brain tumors, called Gliomas instead of brain metastases to predict the duration of their survival. We develop a 3D Convolutional Neural network(CNN) and explore the performances of classical Machine Learning methods with handcrafted features for survival regression of patients with Glioma. The CNN model showed promising results on train data but underperforms and saturates quickly on validation data. More data is necessary for a stable performance of a CNN model for predicting overall survival from MRI sequences. More features need to be extracted from available dataset to achieve better performance with Classical Machine Learning methods.

2 Introduction

Brain metastases are one of the most common neurological complications of cancer and are a major cause of morbidity and mortality[1]. Recent trials have shown that Stereotactic Radiosurgery (SRS) following surgical resection decreases the risk of recurrence by about 50%, and is now the standard of

care for eligible patients. SRS involves using highly focused radiation beams to precise targets that damages the DNA of the target cells. This causes the tumor to shrink as the cells lose their ability to reproduce. SRS has emerged as a safe and effective treatment for patients with limited brain metastases. The most common delayed complication of SRS treatment is radiation necrosis(tissue death), which occurs in approximately 10-15% of treated metastases, typically six months to several years after treatment[2] [3] [4] [5]. Radiation necrosis is often difficult to discern radiographically and clinically from local recurrence and thus determining the duration of survival of patients with lesions is difficult. Surgical resection is often the last option as leaving behind even an insignificantly small portion of the tumor can cause it to re-occur but resecting out extra healthy tissue surrounding the target area can severely compromise brain functionality. Besides, predictions from MRI sequences is subjective and varies with expertise in the field. Thus, there is a need for an unbiased, non-invasive method to solve this problem of classifying lesions at risk for recurrence or radiation necrosis and in turn determining the overall survival of patients from MRI sequences.

The goal of this study is to differentiate between tumor recurrence and radiation necrosis and then predict the overall survival of patients with tumor recurrence. Due to the generic goal of extracting features predictive of survival days from lesions and the ready availability of MRI sequences of patients with Glioma and their survival information, this study uses retrospective database of MRI sequences to develop a Deep Neural Network that can predict overall survival of patients diagnosed with Gliomas instead of brain metastases. Gliomas are the most common types of primary tumors which occur in the brain and spinal cord. Due to their rapid growth and aggressive nature, the survival rate of patients with this diagnosis is low. Having the capability of predicting the approximate survival days from MRI sequences can aid in treatment related decisions and in turn improve patient care. Currently, features are extracted from MRI sequences using Radiomics which are statistical analysed to predict recurrence versus necrosis and the duration of survival. This study provides an opportunity to compare the performance of Deep Learning model with the classical Machine Learning approach to determine the suitable method that can potentially improve patient care.

3 Related work

MRI based Machine Learning strategies have already been successfully implemented in a retrospective fashion for patients with primary lung cancer[6], with deep learning approach proving more predictive than traditional radiomics-based analysis. A similar retrospective effort has been published with primary brain tumors[7] but not for brain metastases. As for the problem of predicting survival days from MRI sequences, it is a relatively new entrant in the field. Several recent papers have begun to study survival regression owing to the Brain Tumor Segmentation(BraTS) 2020[8] competition. The 2nd best perfor-

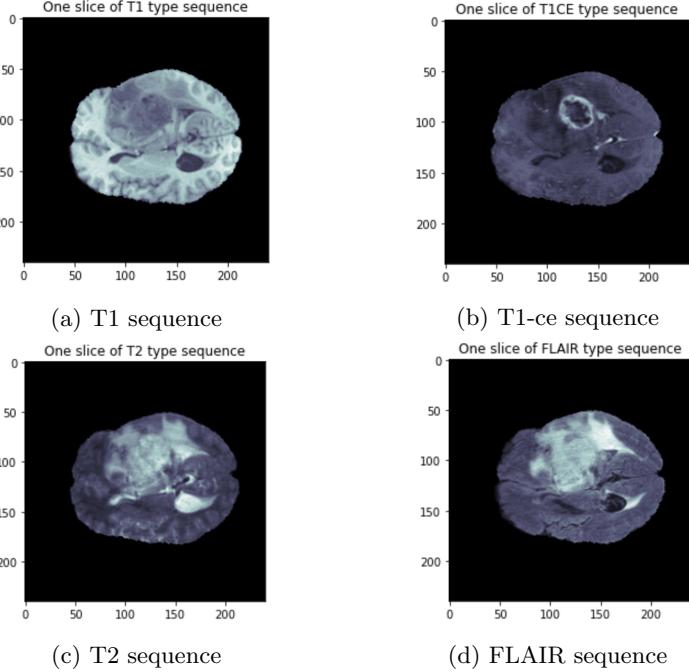


Figure 1: One slice of T1, T1ce, T2, FLAIR sequences each of size 240×240

mance in survival prediction tasks in BraTS 2018 was achieved by Li Sun et al [9]. They used Pyradiomics[10] package to to exact features and used Random Foreset Regression to fit the data. They achieved a promising 61.0% accuracy on classification of short, mid and long survivors with 14 features. Concurrent with our work is that of [11] that explores both Machine Learning and Deep learning methods. They use MRI sequence as input to 3 different 3D Convolutional Neural Network, varying in architecture to achieve accuracies of 37.0%, 39.4% and 44.4% respectively on the validation dataset of 28 samples[11]. Several papers have reported results with ensembles Machine Learning methods on different kinds of radiomics[10] features. Majority of them show good performance on train data but poor performance on validation data. Accuracies hover in the range of 34-62%. Only a handful have attempted the Deep learning approach. To the best of our knowledge, no paper has presented CNN model with sub-volume as input. We attempt to explore and evaluate the performance of Machine Learning methods with fewer extracted features and compare the performances with the published results. We also aim to use 3D CNN with smaller size MRI volumes as input and evaluate its performance.

4 Dataset

The dataset comprising of 370 patients with MRI volumes from T1, T1ce, T2 and FLAIR modalities and survival information is made available by the Brain Tumor Segmentation (BraTS) Challenge 2020.[8]

4.1 Imaging Data

This dataset consists of clinically-acquired pre-operative multimodal MRI scans of glioblastoma and lower grade glioma [8]. All the scans are of size $240 \times 240 \times 155$ pixels and available in NIfTI files(.nii.gz)[12]. Data associated with each patient includes co-registered

- T1-weighted sequence
- Post-contrast T1-weighted (T1Gd) sequence
- T2-weighted (T2) sequence
- T2 Fluid Attenuated Inversion Recovery (T2-FLAIR) sequence
- Manually delineated segmentation mask with ground truth annotations. These annotations comprise the Gadolinium-enhancing tumor (ET — label 4), the peritumoral edema (ED — label 2), and the necrotic and non-enhancing tumor core (NCR/NET — label 1) [8] as observed in Figures 2 and 3.

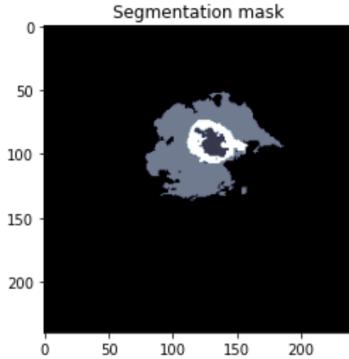


Figure 2: Segmentation mask with each color corresponding to a tumor sub-region annotated with labels 1, 2 and 4. Gadolinium-enhancing tumor — label 4(white), the peritumoral edema — label 2 (light grey), and the necrotic and non-enhancing tumor core - label 1(dark grey).

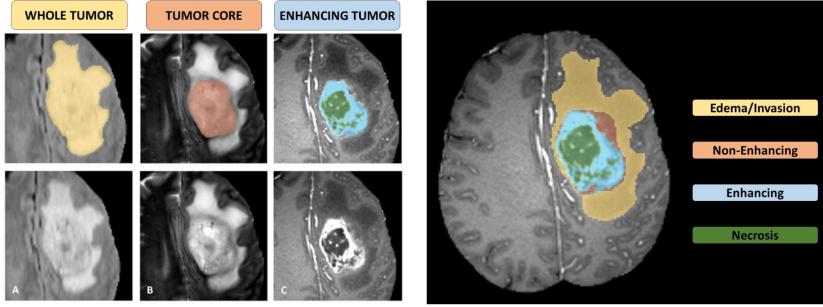


Figure 3: Images with the tumor sub-regions annotated in the different MRI modalities. The image patches show from left to right: the whole tumor (yellow) visible in T2-FLAIR (Fig. A), the tumor core (orange) visible in T2 (Fig. B), the enhancing tumor (light blue) visible in T1-Gd, surrounding the necrotic components of the core (green) (Fig. C)[8].Figure taken from [8].

4.2 Survival Data

The overall survival information, defined in days, are included in a comma-separated value (.csv) file with correspondences to the pseudo-identifiers of the imaging data. The .csv file also includes the age of patients, as well as the resection status of 236 of 370 patients. [8]

5 Data Analysis and Feature Engineering

Basic analysis and understanding of the dataset is essential to make specific decisions about designing Machine Learning and Deep Learning models.

It can be observed that the target variable, Survival Days has an exponential distribution with mean of 445.45 Days as in Figure 4. This mean value will be used for predictions in the baseline model.

We extract additional features such as maximum size of each tumor-subregion from the MRI sequences and plot their distributions as in Figure 5. It can be observed that the sizes are nearly normally distributed. Thus, standardised values can be used for analysis.

Age of patients has normal distribution as in Figure 6 and hence can be standardized to have mean 0 and standard deviation of 1.

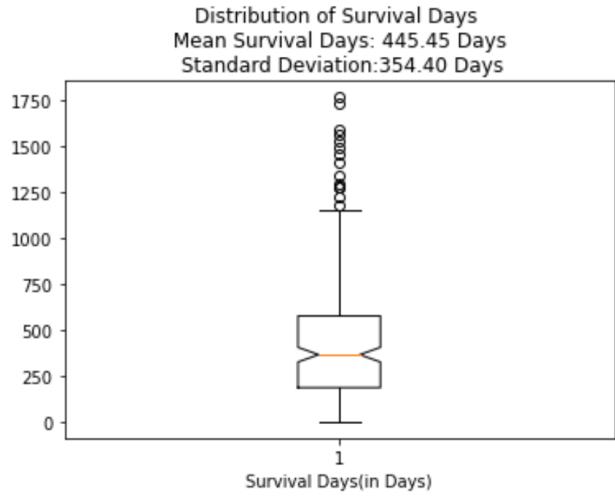


Figure 4: Box plot distribution of Survival Days of the cohort of patients under consideration.

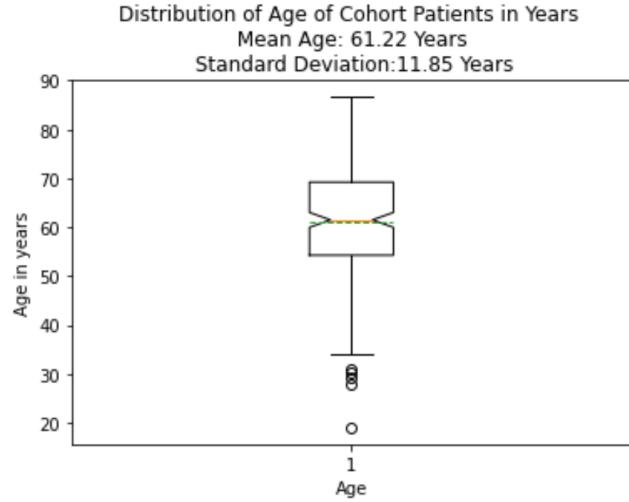


Figure 6: Box-plot distribution of age of cohort of patients under consideration

Age and maximum widths of each tumor sub-region are some of the hand-crafted features that we will use in our algorithms. To understand the importance of each feature in predicting the overall survival, we quantify the correlation between each feature and the survival days using Spearman's correlation

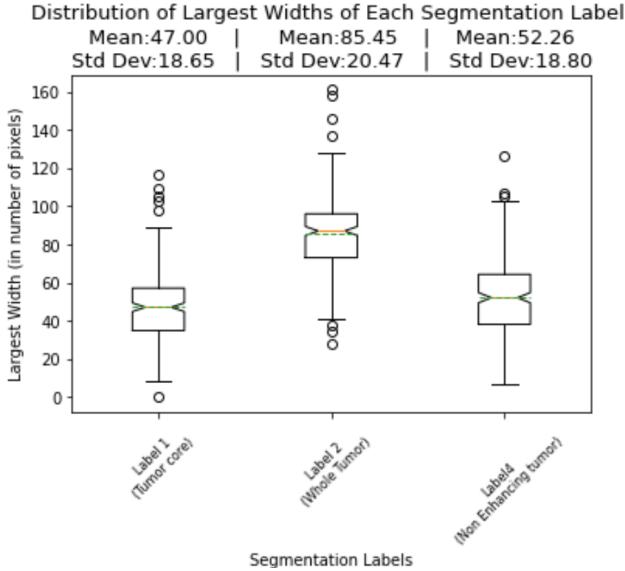


Figure 5: Box plot distribution of the maximum width of each tumor-subregion: Tumor-core(Label 1), Whole tumor(Label 2) and Non-enhancing tumor(Label 4).

coefficient denoted by r_s . It is calculated by[13]:

$$r_s = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

where,

d_i = the difference between the two ranks of each observation

n = number of observations

Spearman's correlation determines the strength and direction of the relationship between two variables that may not be linear. These values range from -1 to 1. Similar to Pearson's coefficient, the signs indicate the direction of relationship(positive implies direct relationship, negative sign implies inverse relationship) while the value indicated the extent of correlation. Figure 7 shows the scatter plot of each feature against survival days.

6 Proposed Method

Some of the established and experimented with techniques to predict survival days are[11]:

- **Classic Radiomics based approach:** Extracting features such as tumor location, shape, texture, gradient information etc., from segmentation

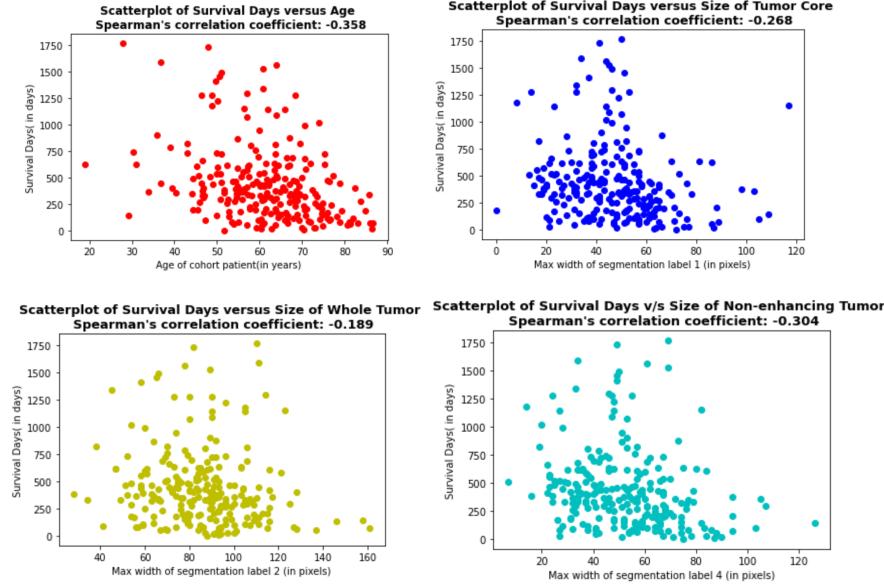


Figure 7: Scatterplot of each feature versus the target variable, Survival days

masks and MRI sequences and performing statistical analysis to predict the approximate duration of survival.

- **Deep Features:** Deep Neural network is used to extract distinguishing features that are then fed to a classic regression model such as Support Vector Machines and Random Forest Algorithms to predict duration of survival.
- **Combination of Radiomics and Deep Neural Network:** Features are extracted from Radiomics and engineered features are fed to a Multi-layer perceptron for prediction.
- **Deep Neural network approach:** Neural networks designed for Regression are fed with imaging and non-imaging data to predict a numeric value for overall survival.

For a thorough exploration of the problem space, we perform experiments ranging from classical Machine Learning models to 3D Convolutional Neural Networks(CNNs).

6.1 CLASSICAL MACHINE LEARNING APPROACH

Classical Machine Learning(ML) techniques often outperform Deep Neural Networks(DNN) when the dataset is small as they have fewer learnable parameters compared to DNNs. Since features are engineered before applying ML

algorithms, this approach improves interpretability and understanding. In our study, we present experiments with Support Vector Regression(SVR) and Random Forest algorithms.

Support Vector Regression uses the same principles as that of Support Vector Machines(SVM) for classification, with minor differences. Since in SVR predictions are real numbers, it is difficult to fit a model that will exactly predict the number. Hence the model aims to fit a hyperplane that minimizes the error with a certain margin of tolerance. Like SVM, SVR also uses different types of kernels: linear, polynomial, radial basis function (RBF) and sigmoid that transform the data into a higher dimension space where the data can be best fit by a hyperplane.

Random Forest Regression: This is an ensemble learning method that involves constructing multiple decision trees during train time and predicting a target value from the constructed decision trees during inference. Random Forest algorithm performs better with sparse training data and is a logical choice in this problem. It also provides features in order of importance which can provide valuable information when there are many features.

6.2 3D CONVOLUTIONAL NETURAL NETWORK(CNN) APPROACH

A 3D Convolutional Neural Network for survival regression task is designed to take in imaging data along with additional clinical data. The Neural Network is designed to predict survival information in days. The following key steps are involved in developing the model.

1. **Data-preprocessing:** The imaging data in the dataset is skull-stripped and centered, thus information is concentrated in the center with little or no significant information in the periphery. Thus, to reduce the number of parameters in the model and to provide the model with a more specific volume to extract features from, a sub-volume of the MRI sequences is extracted. The size of this window is determined by the dataset. Since the primary focus is to extract features from tumor core, we have chosen a sub-volume of size $54 \times 54 \times 54$ which is close to the mean of the distribution of maximum widths of tumor core in the dataset. The maximum width of each tumor sub-region(tumor core, Non-enhancing tumor, edema) along each axis is obtained. Each datapoint(i.e., subject) has associated maximum width values along each of the 3 axes for each tumor sub-section. We are particularly concerned about tumor core and hence use the maximum width values of the tumor core to get the expanse of the tumor and its the centroid. Using the centroid, the boundaries of the sub-volume along each axis are obtained.
Since the number of samples is relatively small for a deep neural network, the above sub-volumes are subject to data-augmentation strategies like scaling, offsetting, rotating, flipping and adding noise to increase the

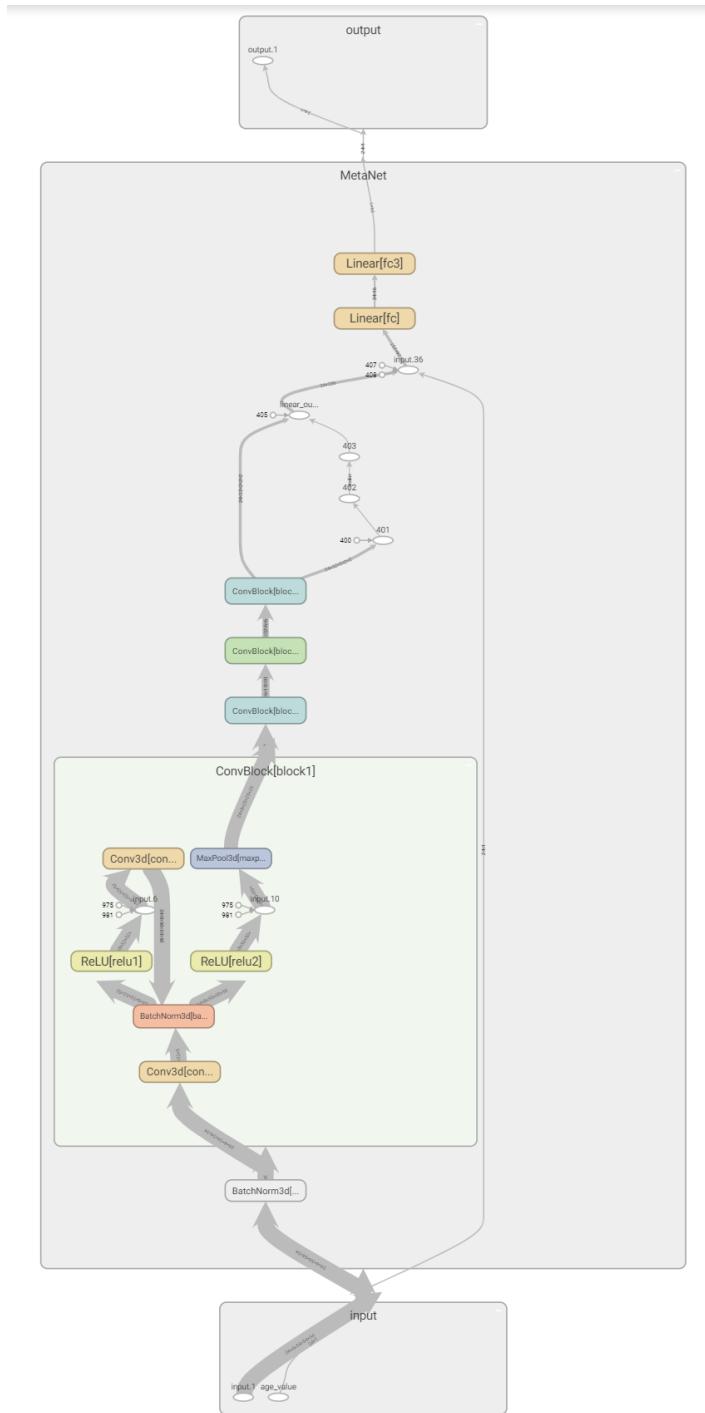


Figure 8: 3D Convolutional Neural Network Architecture

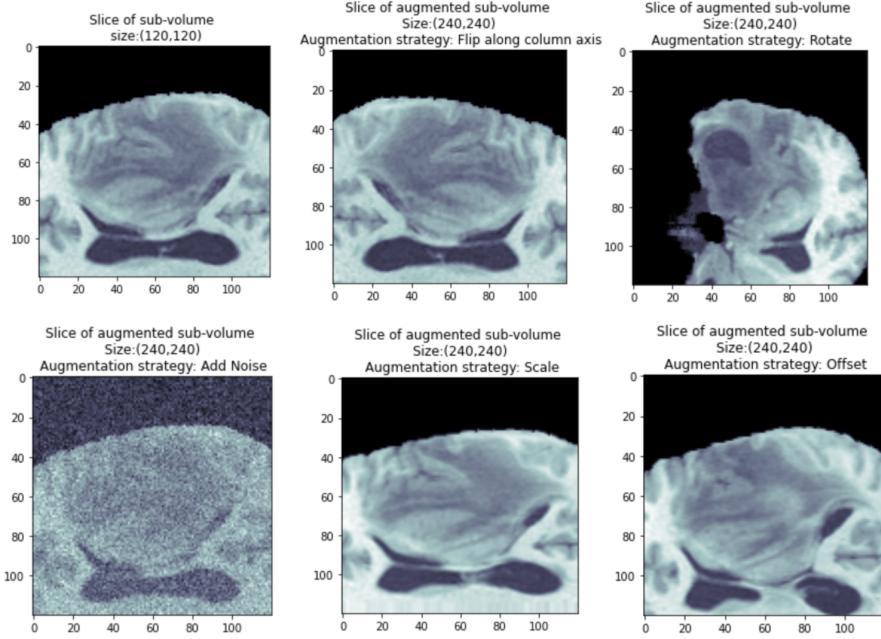


Figure 9: One slice of a datapoint with each augmentation strategy applied individually

dataset samples. Images of a slice of each augmentation strategy can be observed in Figure 9.

2. CNN Architecture Each MRI sequences is volumetric data with size of $240 \times 240 \times 155$. Correlation between slices can provide valuable information on the characteristics of tumor. To retain that correlation, we need the capability of feeding volumetric data to the Neural Network. Hence a 3D convolutional network network is designed. The CNN architecture consists of 4 convolutional blocks each with increasing number of channels, followed by 2 fully connected layers that produces a single regression value. Each convolutional block has two 3D convolutional layers, each of which is followed by a Batch Normalization layer, Rectified Linear Unit layer and a drop-out layer. Translational invariance is achieved with max-pooling at the end of specific convolutional blocks. The model is capable of taking in additional clinical data in the penultimate fully connected layer. It is also designed to take multiple MRI modalities as additional input channels. We use Mean Squared Error and Huber loss as the loss functions.

Mean Squared Error is given by,

$$\text{Loss}_{\text{MSE}} = \frac{\sum_{i=1}^n (y_i - f(x_i))^2}{n}$$

Huber loss is same as Mean Absolute error which becomes quadratic when the error is extremely small. It is given by

$$\text{Loss}_{\text{Huber}} = \frac{1}{2} \sum_i z_i$$

where,

$$z_i = \begin{cases} \frac{1}{2}(y - f(x))^2, & \text{for } |y - f(x)| \leq 1 \\ |y - f(x)| - \frac{1}{2}, & \text{otherwise.} \end{cases} \quad (1)$$

Huber loss is robust to outliers compared to Mean Squared Loss which keeps the model gradients from exploding. We use Stochastic Gradient Descent with learning rate 0.01 and momentum 0.99 and train for 50 epochs. The dataset is divided into 212 train set and 24 validation set and we use a batch size of 32 for better convergence. The model has a total of 114233 trainable parameters.

7 Experiments

All the experiments conducted are compared with the baseline average model, i.e, the Mean Average Error(MAE) and Mean Square Error(MSE) are calculated by predicting the mean survival days for every data-point. The MAE and MSE of the baseline Model are presented in the Table 1.

7.1 CLASSICAL MACHINE LEARNING

1. **Support Vector Regression** We standardise features such as age and maximum width of each tumor sub-region and use non-standardised target, survival days. We fit the data to a Support Vector Regression model with three different kernels: Linear, Radial Basis Function and Polynomial kernel and evaluate Mean Squared Error(MSE) and Mean Average Error(MAE) of each model using 10-fold cross validation on a dataset of 236 patients. The model is L2 regularized with regularization parameter of 0.01. The results are presented in Table 1 without implementing hyper-parameter optimization strategies.
2. **Random Forest Regression** Random Forest Algorithm does not require the features and target values to be standardized. We fit the data to a Random Forest Regression model with an ensemble of 100 trees (arbitrarily chosen). We evaluate Mean Squared Error(MSE) and Mean Average Error(MAE) of the model using 10-fold cross validation. The result is presented in Table 1 without implementing hyper-parameter optimization strategies.

METHOD	MSE in Days ²	MAE in Days
Baseline Average Model	125602.76	258.82
Support Vector Regression(Kernel='linear')	113680.55	224.97
Support Vector Regression(Kernel='rbf')	120120.42	261.49
Support Vector Regression(Kernel='poly')	123003.82	283.98
Random Forest Regression	122434.32	257.96

Table 1: Tabulation of 10-fold cross validation MSE and MAE results for different Machine Learning Techniques.

7.2 3D CONVOLUTIONAL NEURAL NETWORK

A series of experiments were conducted with architectural differences, hyper-parameter tuning and different augmentation strategies. In general, augmentation, Batch Normalization and Drop-out strategies improved the performance of the model while L2 regularization showed varying performance.

Taking whole Tumor label into consideration, experimentation with architectures for sub-volume sizes of 48, 64, 70, 80, 90 and 120 with T1 sequences as input yielded sub-volume sizes in the range of 48 - 80 as optimal. The MAE loss for train and validation losses are shown in Figure 10.

The different MRI modalities provide complementary information owing to the different contrasts that are used in the process of capturing information. Experiments were conducted with different MRI modalities as inputs to find a modality that better predicts survival of a patient. These experiments are presented in Figure 11. T1 sequences performed marginally better compared to the other sequences on train data but no sequence produced distinguishing results with validation set.

It was observed that the weight updates and predictions in every epoch were all in the same range which contributed to large errors. To counter this problem, the loss function was changed to Mean Square Error Loss. Each data-point was normalized as per its z-score to avoid gradients from exploding and tumor core label was used instead of whole tumor.

Since it was previously observed that age has high correlation with survival days, experiments were conducted to compare models with and without age of patient as input. Figure 12 depicts the MAE and MSE loss curves with and without age as input.

To improve the generalization power of the model, experiments were conducted with different MRI modalities stacked up as channels. Since these modalities provide complimentary information, this stacking can be treated similar to different color planes stacked in RGB images. The performance of a model with T1ce as input is contrasted against a model with all sequences stacked as channels and fed as input in presented in Figure 13.

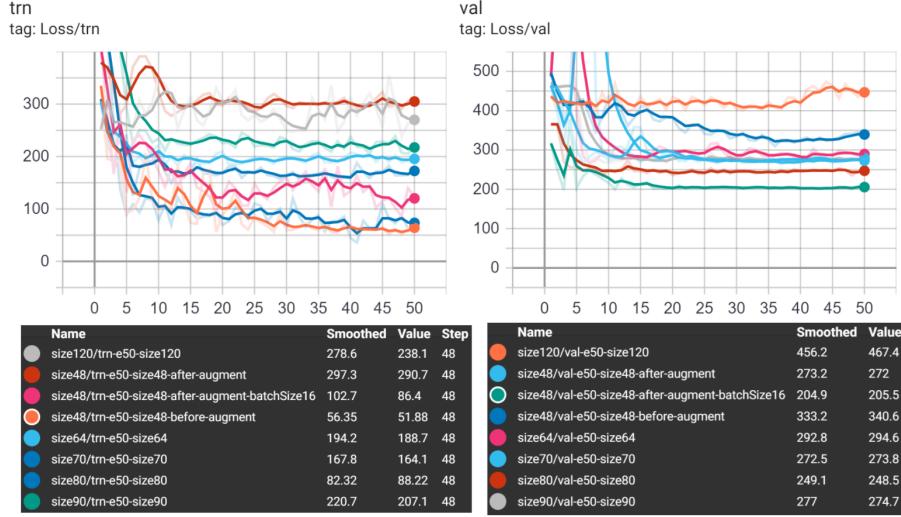


Figure 10: Train and Validation MAE curves of the network designed for sub-volumes of sizes 48, 64, 70, 80, 90 and 120 shown in different colors. In all the experiments the train loss converges quickly to reasonably low values but validation loss saturates quickly leaving a wide gap between train and validation losses.

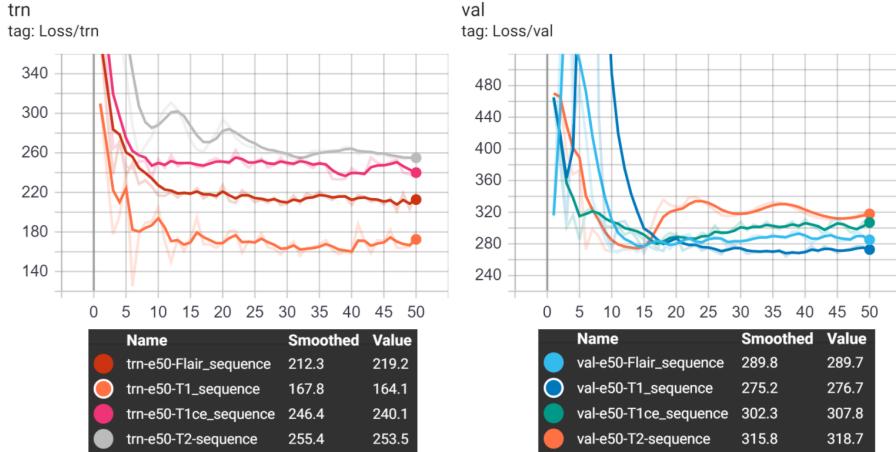
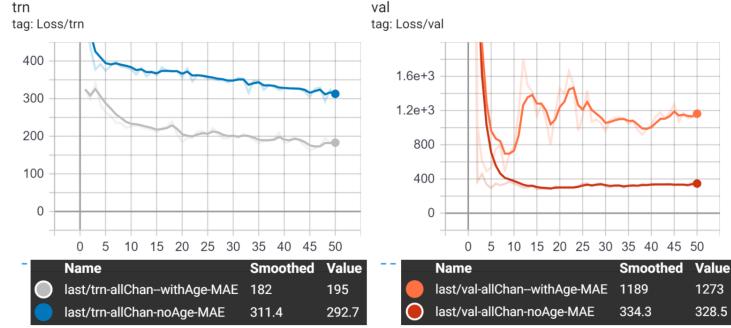
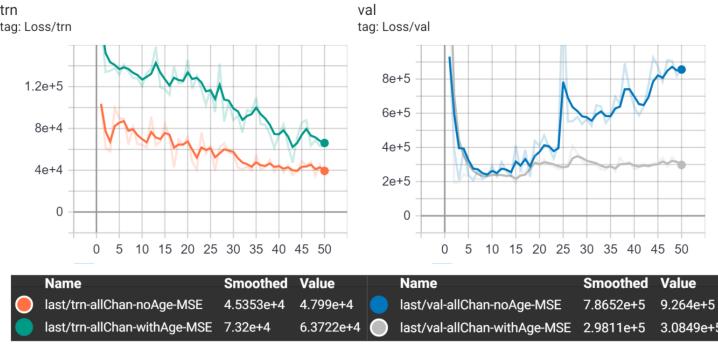


Figure 11: From left to right:train and validation loss plots for different MRI modalities(T1, T2, T1ce and FLAIR). Model with T1 sequence as input produced lowest loss with train data but no appreciable difference in performance with respect to validation set.

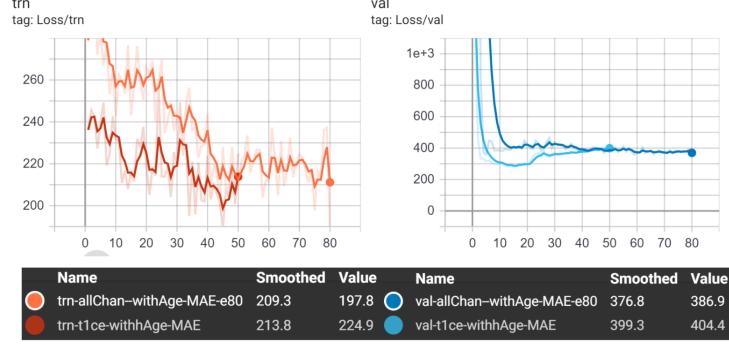


(a) MAE train and validation loss plot for models with and without age as input

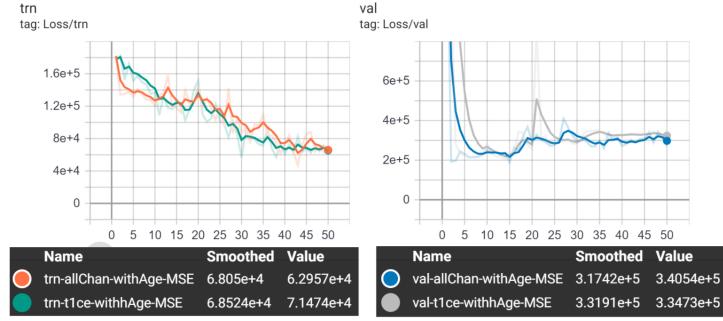


(b) MSE train and validation loss plot for models with and without age as input

Figure 12: MAE (top) and MSE (bottom) train and validation loss plot for models with and without age as input. In general, age improved the performance of the model.



(a) MAE train and validation loss with all sequences stacked as channels versus only T1ce sequence as input



(b) MSE train and validation loss with all sequences stacked as channels versus only T1ce sequence as input

Figure 13: Shows the plot of MAE (top) and MSE (bottom) train and validation loss plots with a single sequence (T1ce) versus all sequences stacked as channels

8 Discussion/Interpretation

It is known that classical Machine Learning Algorithms perform better than Deep Learning models when the dataset is small as they have fewer learnable parameters needed to generalise to the dataset. This trend can be observed in this study as well. Some points worth noting in this investigation are as follows.

1. There is scope for improved learning with classical Machine Learning methods as it can be observed that the SVR with linear kernel and Random Forest Algorithm, without any hyperparameter tuning beat the average baseline model with just 4 features. Extracting more features can possibly improve the performance.
2. 3D convolutional neural network have more representative power but the number of train and validation samples are quite low. Reducing the com-

plexity of the model reduced the representational capability of the model and increasing the complexity increases the gap between train and validation losses.

3. When the whole tumor label is considered, sub-volume of size 48 - 80 produced good results. Architecture with a sub-volume of size 80 marginally beats the baseline statistics.
4. Augmentation significantly improved the performance but as the size of sub-volume increased the generalization capacity of the model reduced thus producing poor results.
5. Different MRI modalities provide complementary information but neither appeared to significantly outperform the others. The convergence losses were nearly in the same range for T1, T1ce, T2 and FLAIR sequences which hints at the predictive power of MRI sequences in survival regression.
6. Stacking channels added large number of parameters but improved the generalization capacity of the model only slightly. Due to large number of parameters and insufficient data, the model overfit the available data.
7. The correlation between age and survival information proved useful. Model with age and MRI sequence as input performed appreciably better than models with only imaging data as input.
8. A common problem in all these experiments is overfitting. It can be observed that the loss of even the best models are relatively high. Apart from insufficient data, this can be attributed to the inherent difficulty and uncertainty in predicting the duration of survival after resection as the extent of resection and patient's response to treatment significantly contributes to overall survival. MRI sequences not being predictive of overall survival could also be the reason for such low performance. Besides, MRI sequences are obtained by reconstruction. The noisy nature of the modality may not be appropriate for this problem. There is simple not enough data to provide definitive results.

9 Conclusion

CNN models provide promising but not conclusive results. With more information, we would have been able to explain if MRI sequences are representative of overall survival or not. It was observed that classical Machine Learning model performances using only tumor size and age information beat the baseline models. In any case, extracting more features from the existing dataset can help improve the performance. We hypothesize that adding post-treatment imaging data and more clinical information to the dataset would boost the performance of the survival regression. With more data, CNN could perform better.

10 Future Direction

- To incorporate more data into the model, we can look for pattern with pre and post resection sequences and use additional information such as different modalities serving as data points, clinical data, biopsy information etc.
- In all the above experiments, we have chosen a standard sized sub-volume for every tumor irrespective of its volume. Another area to explore is to take the entire volume of the sub-section and resize to a standard sub-volume size.
- Work is underway in formulating this problem as a classification problem instead of a Regression problem with patients categorised into three class: low risk, medium risk and high risk categories.

11 Resources

11.1 Software

The model is built on PyTorch[14] using necessary PyTorch libraries. We used Jupyter notebook[15] and Pycharm for code editing and execution on personal systems and Google Colaboratory[16] to run model on GPU.

11.2 Hardware

Computer hardware that we have used has the following configuration

- Asus Vivobook Pro - NVIDIA GeForce GTX 1050 with 4GB RAM

12 Acknowledgment

We would like to thank Dr. Matthew Malloy and Dr. Alan MacMillan for their valuable advice and guidance throughout the project.

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