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ARAŞTIRMA / RESEARCH

The success of machine learning algorithms developed with radiomic features obtained from preoperative contrast-enhanced MRI in the prediction of short-term survival in patients with Glioblastoma

Glioblastomlu hastalarda kısa dönem sağkalımı tahmininde preoperatif kontrastlı MRG'den elde edilen radyomiks özelliklerle geliştirilen makine öğrenme algoritmalarının başarısı

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Abstract

Purpose: This study aimed to evaluate the predictability of survival in patients with glioblastoma using a machine learning (ML) model developed with tissue analysis features obtained through preoperative post-contrast T1-weighted images(T1WI).

Materials and Methods: The radiomic features of tumors were obtained from postcontrast T1WI of 60 glioblastoma patients. Radiomic properties, density, shape, and textural properties obtained from six matrices were included in the analysis. The patients' three- and six-month survival rates were recorded. Five different ML algorithms were applied to create predictive models [random forest, neural network, linear discriminant analysis(LDA), stochastic gradient descent (SGD), and support vector machine(SMV)].

Results: The mean survival time of the patients was 295.4 days, and the median value was 211.5 (17-1357) days. Among the models developed for three- and six-month survival prediction, the highest success was obtained from the LDA algorithm, in which the AUC values were calculated as 0.88 and 0.78, respectively.

Conclusion: Using ML techniques, the success of predicting imaging-based patient survival was very high. With the development and widespread adoption of these techniques, ML models will be useful in deciding on treatment according to survival prediction in glioblastoma.

Keywords: Glioblastoma, machine learning, texture, MRI

Öz

Amaç: Bu çalışma ameliyat öncesi kontrastlı T1 ağırlıklı görüntülerden(T1AG) elde edilen doku analizi(radyomiks) özellikleriyle geliştirilen makine öğrenimi(MÖ) modeli kullanılarak glioblastomlu hastalarda sağkalımın öngörülebilirliğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Tümörlerin radyomiks özellikleri 60 glioblastoma hastasının kontrastlı T1AG'den elde edildi. Altı matristen elde edilen radyomik özellikler, yoğunluk, şekil ve dokusal özellikler analize dahil edilmiştir. Hastaların üç ve altı aylık sağkalım oranları kaydedildi. Tahmine dayalı modeller [random forest, neural network, linear discriminant analysis(LDA), stochastic gradient descent (SGD), support vector machine(SMV)] oluşturmak için beş farklı MÖ algoritması uygulandı.

Bulgular: Hastaların ortalama sağkalım süresi 295,4 gün, medyan değeri 211,5 (17-1357) gündü. Üç ve altı aylık sağkalım tahmini için geliştirilen modellerden en yüksek başarı, EAA değerlerinin sırasıyla 0,88 ve 0,78 olarak hesaplandığı LDA algoritmasından elde edilmiştir.

Sonuç: MÖ tekniklerini kullanarak, görüntülemeye dayalı hasta sağkalımını tahmin etme başarısı çok yüksekti. Bu tekniklerin gelişmesi ve yaygınlaşması ile MÖ modelleri, glioblastomda sağkalım tahminine göre tedaviye karar vermede faydalı olacaktır.

Anahtar kelimeler: glioblastom, makine öğrenmesi, texture, MRG

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INTRODUCTION

Glioblastoma is the most common primary malignant brain tumor in adults with an estimated annual incidence of 0.6 -3.7/100,000 cases per year, varying from one country to another[1]. Chemoradiotherapy is applied after surgery in the treatment of glioblastoma. Patients die within weeks or months after these treatments, the median life span varies between 11 and 15 months, although some patients are known to live for more than 36 months[2,3].

Magnetic resonance imaging (MRI) plays a critical role in the initial diagnosis of glioblastoma, evaluating the treatment response, and is increasingly a powerful non-invasive predictive tool. Many studies have identified relationships between MRI features and survival in patients with high-grade glioma[4,5]. Radiomics has been proposed to evaluate and investigate the biology, genetics, and molecular properties of tumoral tissue using medical images. Radiomics term to a process that extracts highly efficient quantitative features from radiographic images and constructs predictive models for classifying image characteristics into genomic properties and clinical consequences[6]. Nowadays, several radiology models based on radiomics, such as metastasis prediction, survival prediction and classification of molecular and genetic properties, have been proposed[7-9]. It should be kept in mind that according to the radiomics hypothesis, imaging heterogeneity may be an output of underlying genetic heterogeneity[10]. Also, recently, machine learning models based on texture analysis have been developed. Machine learning consists of a large class of statistical analysis algorithms developed iteratively in response to training data to create models for independent predictions[11]. Rapidly growing computer technology is used in machine learning in object detection, placement, and classification in many digital images. The use of machine learning in the field of radiology is also increasing. Recently, machine learning models have been used to predict survival or distant organ metastasis in prostate and breast cancers based on MRI and in non-small-cell lung carcinoma based on computed tomography[8,12,13].

In glioblastoma, conventional imaging methods have little chance of success in predicting survival. Previous studies in the area performed survival prediction based on texture features obtained from perfusion mapping images[14]. Although these procedures are academically successful, they are challenging to apply to huge patient series and multicenter research. In this respect, there is a need for evaluations to be made over a single sequence that can be reached more easily and quickly. Thus, this study aimed to investigate the predictability of especially the short-term survival of patients using a machine learning model developed with tissue analysis features obtained from preoperative contrast-enhanced T1-weighted images.

MATERIALS AND METHODS

The local institutional review board approved this retrospective study (decision/protocol number 2020/722, Adana Teaching and Research Hospital Ethics Committee). The written informed consent was obtained from the participants enrolled in this study. Before the radiological examination, written informed consent was received from each patient (parents or guardians of patients aged <18 years).

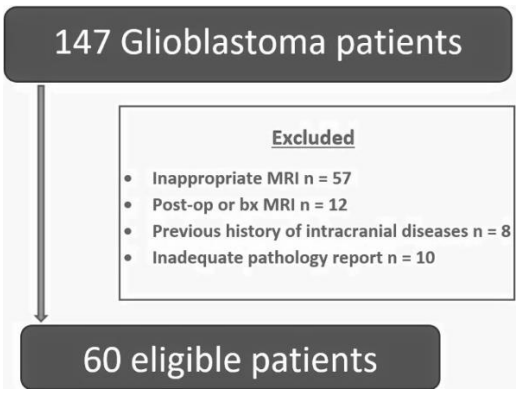

Figure 1. Patient selection and exclusion criteria

Patient selection

Patients histopathologically diagnosed with glioblastoma between January 1, 2016, and October 30, 2019, were retrospectively screened from the records of Adana Teaching and Research Hospital. Patients who were diagnosed with WHO grade 4 glioblastoma based on the pathology report, underwent MRI before surgery and had at least six months between their diagnosis and the time of the study were included. Excluded from the study were patients with other intracranial diseases (severe traumatic brain injury, severe infection and other benign/malign brain tumors), those with MRI images that contained motion artefacts, those treated before

imaging, and those having a glioblastoma grade other than grade 4 according to 2016 WHO pathological calcification system (Fig 1.).

MRI acquisition

Post-contrast 3D T1 images of all patients participating in the study were evaluated. The patients were scanned using 1.5 T Philips Ingenia (Philips Medical Systems, Amsterdam, Netherlands) and GE Optima 360 (GE Medical Systems, Milwaukee, Wis) devices. Three-dimensional T1-weighted images (6.3/3.1; field of view, 240 mm; section thickness, 1 mm; matrix, 192x192) were acquired after the administration of a gadolinium-based contrast agent (0.1 mL/kg gadobutrol, Gadovist; Bayer, Toronto, Ontario, Canada). The three-dimensional data of postcontrast T1-weighted MRI were collected during the continuous interval of 90–250 s.

Texture extraction

In this study, Lifex (http://www.lifexsoft.org, LITO, CEA, Inserm, CNRS, Univ. Paris-Sud, Université Paris Saclay) software was used to extract the texture properties. Post-contrast 3D T1-weighted images of the patients were analyzed. The patients' images were evaluated independently by a specialist radiologist with four years of experience and a three-year radiology assistant who had completed primary neuroradiology training. The region of interest (ROI) was manually drawn in all planes without including vasogenic edema in the contrast-enhanced outer boundaries of the tumor. After the ROI delineation, texture features were calculated automatically using default settings (128 discrete gray levels. All fundamental statistical analyses were performed using SPSS software version 24.0 (SPSS Inc.), and p-value of less than 0.05 were considered to indicate significant differences.

A total of 49 texture features were extracted from the MRI images, including first-order statics (minValue, meanValue, maxValue, and stdValue, histogram parameters) and parameters were derived from five matrices: gray-level co-occurrence matrix (GLCM), shape, gray-level run-length matrix (GLRLM), gray-level zone length matrix (GLZLM), and neighborhood gray-level dependence matrix (NGLDM).

The procedure was implemented twice by a specialist radiologist and a radiology resident to provide reproducibility of the extraction. The reliability of texture features was evaluated with the intraclass correlation coefficient. Intraclass correlation coefficient cut-off for good reproducibility was 0.80. However, for a more accurate evaluation, the arithmetic mean of both measurements was taken, and this value was used in further analyses.

Statistical analysis

A large number of texture property data of 60 patients had to be processed before entering them in the machine learning algorithms. This process was carried out in several stages. In the first stage, standardization of data was performed, followed by a co-linearity analysis (features displaying a strong correlation ($r>0.8$) were removed. Then, the data sample was stratified using a 10- fold cross-validation technique along with minority oversampling. In the last stage, statistically non-significant data were eliminated to avoid overcompliance, shorten the time required for modeling, and increase accuracy. For this purpose, two different feature selection methods, namely Gini index and ReliefF algorithms were used. According to both algorithms, six common features with the highest success were selected.

The patients were divided into two groups according to three-month and six-month survival. Machine learning models were created separately for each group to predict survival. Machine learning-based classifications were performed using the Waikato Environment for Knowledge Analysis (WEKA) toolkit version 3.8.3. Five different machine-learning algorithms for binary classification were evaluated: random forest, neural network, stochastic gradient descent (SGD) method, linear discriminant analysis (LDA), and support vector machine (SMV). Model performance was internally validated using a 10-fold cross-validation protocol (Fig. 2). Performance evaluation was undertaken using the area under the curve (AUC) analysis. Accuracy, recall, precision, and F-measure (weighted-harmonic mean of precision and recall) coefficients were obtained. In addition, models were developed to evaluate the overall survival prediction success of the models. For this purpose, GLCM Entropy-log10, which is the most successful parameter used in machine learning models, was used. GLCM Entropy-log10 was dichotomized based on an optimum cut-off value derived from the receiver operating characteristic (ROC) analysis. Then, the Kaplan-Meier model was constructed based on this value.

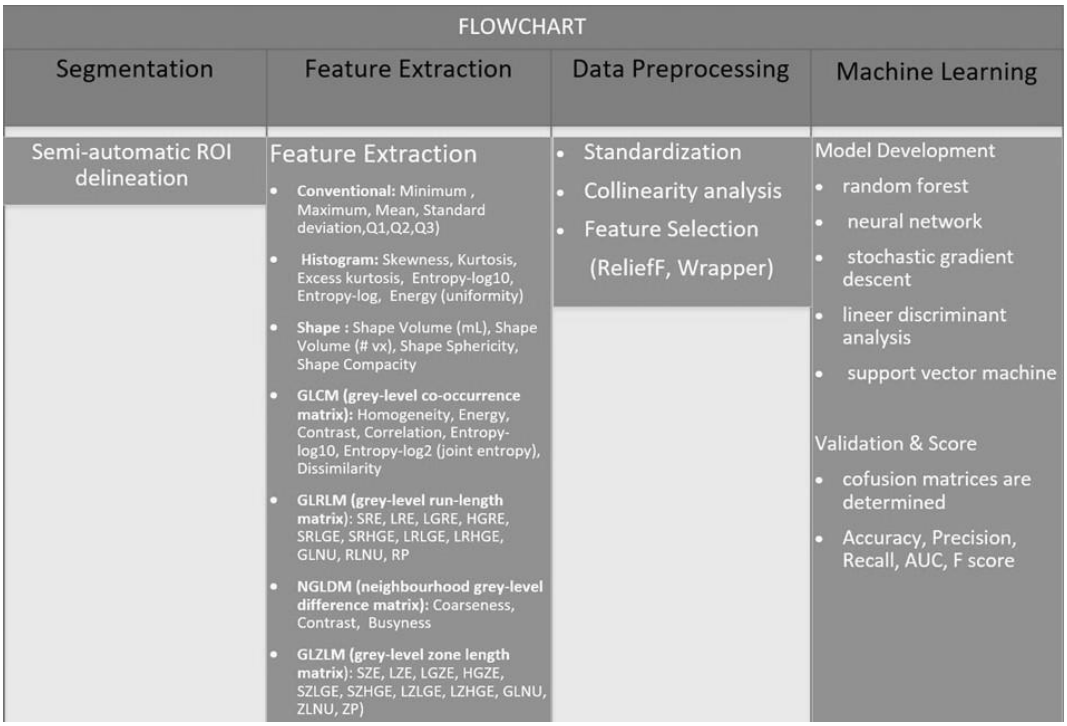

Figure 2. Overall flowchart of the proposed method.

Table 1. Success of three-month survival prediction models developed by ML algorithms

ML algorithm	ACC (%)	PREC (%)	RECALL (%)	F score (%)	AUC	Confusion Matrix		Outcome
						Predict mortality	Predict survival	
LDA	95	92	85	0.88	0.887	11	2	died
		96	98	0.97		1	46	survived
Neural	93.33	85	85	0.85	0.872	11	2	died
Network		96	96	0.96		2	45	survived
Random	93.33	85	85	0.85	0.872	11	2	died
Forest		96	96	0.96		2	45	survived
	95	92	85	0.88	0.887	11	2	died
SGD		96	98	0.97		1	46	survived
	81.67	67	31	0.42	0.633	4	9	died
SMV		83	96	0.89		2	45	survived

ML: machine learning, LDA: linear discriminant analysis, SGD: stochastic gradient descent, SMV: support vector machine, Prec: precision, ACC: accuracy, AUC: Area Under the Curve

RESULTS

Sixty patients who met the necessary inclusion criteria were evaluated in the study. The mean age of the patients included in the study was 53 (5-89) years. All the patients underwent appropriate surgical tumor resection using the standard treatment protocol after diagnosis. Of the patients included in the study, 39 were male, and 21 were female.

According to the patients' pathology reports, 12 were consistent with IDH mutant type and 48 patients with IDH wild type glioblastoma. The mean survival time of the patients was 295.4 days, and the median value was 211.5 (17-1357) days. There was no

significant difference in the mean survival time between males and females.

Among the models developed for the prediction of three-month survival, the highest success was obtained from the LDA and SGD algorithms. Six features were selected according to the Relieff and Wrapper algorithms. For the six-month survival prediction modeling, the LDA algorithm achieved the highest success using the six features chosen according to the Relieff and Wrapper algorithms. Each model's performance for the three-month and six-month survival prediction is presented in Tables 1 and 2, respectively (including precision, recall, accuracy, and AUC). Figure 3 presents the Kaplan-Meier curve obtained based on the cut-off value calculated using the ROC analysis, as well as the log-rank values, Table 3 shows the Breslow Tarone-Ware values, and Table 4 summarizes the median and median survival data.

Table 2. Success of six-month survival prediction models developed by ML algorithms

ML algorithm	ACC (%)	PREC (%)	RECALL (%)	F score (%)	AUC	Confusion Matrix		Outcome
						Predict mortality	Predict survival	
LDA	83.33	86	72	0.78	0.782	18	7	died
		82	91	0.86		3	32	survived
Neural	75	73	64	0.68	0.729	16	9	died
Network		76	83	0.79		6	29	survived
Random	75	78	56	0.65	0.755	14	11	died
Forest		74	89	0.80		4	31	survived
	81.66	85	68	0.76	0.797	17	8	died
SGD		80	91	0.85		3	32	survived
	66.67	67	40	0.50	0.629	10	15	died
SMV		67	86	0.75		5	30	survived

ML: machine learning, LDA: linear discriminant analysis, SGD: stochastic gradient descent, SMV: support vector machine, Prec: precision, ACC: accuracy, AUC: Area Under The Curve

Table 3. Log-rank, Breslow and Tarone-Ware values according to the overall comparison of GLCM entropy log10

GLCM Entropy Log10 Overall Comparison			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.067	1	0.024
Breslow (Generalized Wilcoxon)	8.711	1	0.003
Tarone-Ware	6.96	1	0.008

Test of equality of survival distributions for the different levels of GLCM228; GLCM: gray-level co-occurrence matrix

Table 4. Mean and median survival times divided into two groups according to the GLCM entropy log10 values of < and > 2.28

Mean and Median Survival Times								
	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
GLCM entropy log10 < 2.28	590.63	107.89	379.16	802.1	359	94.65	173.48	544.51
GLCM entropy log10 > 2.28	269.27	44.9	181.25	357.28	157	43.63	71.46	242.53
Overall	439.68	70.1	302.26	577.09	237	75.71	88.6	385.39

a. Estimation is limited to the largest survival time if it is censored.; GLCM: gray-level co-occurrence matrix

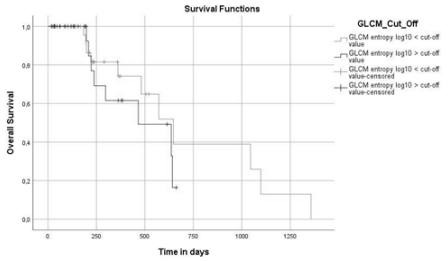

Figure 3. The Kaplan-Meier curve in which the survival times are divided into two groups according to the GLCM entropy log10 cut-off value.

DISCUSSION

It is very difficult to assess the histological grades of glial tumors, determine their molecular subtypes, and predict patient survival through conventional preoperative imaging methods. Therefore, in recent years, the development of machine learning models based on texture analysis methods has led to the re-evaluation of many parameters. In neuroradiology, machine learning models have started to be used in grading glial tumors. Especially in the preoperative period, to predict molecular subtype and survival[15-18]. Our study developed a machine learning model for predicting survival based on texture analysis data obtained from contrasted T1-weighted images obtained in the preoperative period. The developed algorithms belonged to the LDA, neural network, random forest, SGD, and SMV methods. Among these methods, LDA provided the model with the highest three- and six-month survival estimates in the patients' preoperative images (other models presented in Tables 1 and 2). The three- and six-month AUC values were 0.88 and -0.78, respectively, and the accuracy values were 95% and 83.3, respectively. LDA is a classification method developed by Fischer in 1936. Despite being simple, it is a model that produces good results in complex problems. It is a statistical classifier that combines the entered parameters into a distinctive function to classify situations in different groups[19]. Our results showed that the LDA-based model had promising performance in predicting survival in glioblastoma. In the evaluation performed with the conventional survival analysis method, we found that GLCM entropy alone was very successful in survival prediction, especially in the early and medium terms. However, when we examined the findings obtained with confidence intervals, they fell behind those of machine learning models.

Considering the previous literature, studies have been carried out to predict survival in glioblastoma using texture-based machine learning models. In a survival and subtyping study based on the multiparametric images of 134 glioblastoma patients, Macyszyn et al.[20] calculated the AUC of SMV model as 0.79. In another survival analysis based on dynamic susceptibility contrast-enhanced images in 24 glioblastoma patients, Lee et al.[14] found the AUC as 0.849. Prasanna et al.[21] determined the concordance(C) index as 0.67 in random forest models in long- and short-term survival prediction in 65 glioblastoma patients based on radiological features obtained from the peritumoral brain parenchyma in multi-parametric MRI.In another study, Being et al.[22] found the C-index as 0.83 for the survival prediction based on contrast-enhanced T1, T2, and FLAIR images in 115 glioblastoma patients. In the current study, the AUC values were calculated 0.88 and 0.82 for the prediction of three- and six-month survival. The follow-up period was six months in some of the previous studies and 18 months in others. Furthermore, no standard algorithm was used in those studies. Although the methods and models of all these studies differed, the success of machine learning models in predicting survival was consistently high.

Some studies focused on identifying factors affecting prognosis before treatment in patients with glioblastoma[22]. Resection degree, necrosis grade, patient age, and Karnofsky performance status (KPS) have been evaluated to estimate the survival times of glioblastoma patients[23]. Among these, especially KPS has started to be used as a prognosis criterion in recent years[24]. However, KPS has internal inconsistencies, and there are both practitioner- and individual-based contradictions[25, 26]. Therefore, more objective and standardized methods are required to predict survival before treatment in glioblastoma patients, and they should be considered when evaluating treatment options. Although glioblastoma patients' survival time is concise, all treatment methods should be taken into consideration in the decision-making phase of treatment options, especially for patients with a life expectancy of more than six months.

In our study, we aimed to predict early survival specifically. Unfortunately, curative treatment is not generally possible with current medical and surgical

approach methods in glioblastoma. Therefore, the main goal in treatment is to increase the average survival and palliation. Thus, the life expectancy of patients is critical. When we examined our findings, LDA modeling was found to have a much higher success in predicting patient survival for three and six months than predicting mortality (three months recall: 98%, six-month recall: 91%). In this situation where life expectancy is critical, these findings were very promising in encouraging and directing the patient and clinician.

Although our results are promising, our study has some limitations, one of which was the use of CE 3D T1-weighted images alone. However, our analysis revealed the high prognostic value of this single MRI scan contrast. In addition, tumor segmentation was performed in a time-consuming and user-dependent manner. This underlines the need for automated tumor segmentation, which will minimize user bias and allow larger-scale studies. Another limitation is that the sample size was small, and the study had a single-center and retrospective design. In the future, large-scale multicenter studies are needed to assess the generalization ability of radiomic models fully. Due to our study's small sample size, we were unable to divide our data into training and test data sets. To overcome this problem, 10-fold cross-validation was used, thereby providing an unbiased estimate in this sample. Nevertheless, further studies in independent data sets are required to ensure that our approach can be generalized with independent data. Studies with study models and results similar to our study are available in the literatüre[19-21]. However, the number of studies with successful results based on radiomics in many cancer types is increasing day by day. Radiomics has become an obligation to demonstrate that the features are reproducible in different centers as much as success and standardization.

In this study, the machine learning models developed based on the texture analysis of data obtained from contrast-enhanced T1-weighted images had very high success in predicting three- and six-months survival in glioblastoma patients. The addition of complementary imaging parameters in future studies can further improve survival estimation using radiomic analysis. In addition, machine learning models to be developed with the independent verification of radiological features can help decide on an appropriate treatment according to survival prediction in patients diagnosed with glioblastoma.

Yazar Katkıları: Çalışma konsepti/Tasarımı: OD, ED; Veri toplama: OD, ED; Veri analizi ve yorumlama: OD, ED, EB, BBD,BG; Yazı taslağı: OD, ED; İçeriğin eleştirel incelenmesi: OD, ED, EB, BBD, BG; Son onay ve sorumluluk: OD, ED, EB, BBD, BG; Teknik ve malzeme desteği: OD, ED, EB; Süpervizyon: -; Fon sağlama (mevcut ise): yok.
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