Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2025;50(3):661-672
DOI: 10.17826/cumj.1661241

RESEARCH

Prediction of prognosis in brain metastasis with artificial-intelligence-driven methods for whole brain radiotherapy

Beyin metastazında tüm beyin radyoterapisi sonrası yapay zeka destekli prognoz tahmini

Emine Elif Özkan[1], Tekin Ahmet Serel[2]

[1]Suleyman Demirel University, Isparta, Türkiye

Abstract

Purpose: Inferentially, 24%–45% of cancer patients develop brain metastases in their course. Individual survival estimation for these patients is crucial to identify the subset that may not benefit from whole-brain irradiation (WBI) due to a short survival time. This study aimed to identify variables and evaluate an artificial intelligence algorithm to determine which patients would benefit from WBI.
Materials and Methods: The data of 345 patients with brain metastasis who were treated with 30 Gy in 10 fractions of WBI were retrospectively analyzed. In this cohort, a total of 15 clinical / laboratory factors are evaluated with 15 models of machine learning algorithms using Python 2.3, Pycaret library.
Results: The Gradient Boosting Regressor was found to be the most accurate model, with a 0.68 R2 an R^2 value of 0.68, and a mean absolute error (MAE) of 12.90.The prediction error for the gradient Boosting Regressor was calculated as R2: 0.841. When the importance of features was investigated, time from diagnosis to metastasis was found to be the most important predictive variable for survival.
Conclusion: The results of this study enable us to identify patients who may have an early death and provide a consequential decision guide in terms of whole-brain radiotherapy or additional labor-intensive techniques.

Keywords: Brain metastases, machine learning, prognosis, radiotherapy, survival.

Öz

Amaç: Çıkarımsal olarak kanser hastalarının %24-45'i, seyirleri sırasında beyin metastazları geliştirir. Bu hastalar için bireysel sağkalım tahmini, kısa sağkalım süresi nedeniyle tüm beyin ışınlamasından (WBI) fayda görmeyebilecek hasta alt grubunu ayırt etmek için önemlidir. Bu çalışma, değişkenler üzerinde arama yapmayı ve WBI'dan fayda görecek hasta alt grubunu belirlemek için bir yapay zeka algoritmasını değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: 10 fraksiyonda 30 Gy WBI ile tedavi edilen beyin metastazı olan 345 hastanın verileri retrospektif olarak analiz edildi. Bu kohortta toplam 15 klinik/laboratuvar faktörü, Python 2.3, Pycaret kütüphanesi kullanılarak 15 makine öğrenme algoritması modeli ile değerlendirildi.
Bulgular: Gradient Boosting Regressor'un 0,68 R2 değeri ve 12,90 ortalama mutlak değer (MAE) ile doğru modelleme olduğu bulundu. Gradient Boosting Regressor için tahmin hatası R2: 0,841 olarak hesaplandı. Özelliklerin önemi incelendiğinde, tanıdan metastaza kadar geçen sürenin sağ kalım için en önemli öngörücü değişken olduğu bulundu.
Sonuç: Bu çalışmanın sonuçları erken ölüm riski olan hastaları belirlemeyi mümkün kılıyor ve tüm beyin radyoterapisi veya ek emek yoğun teknikler açısından sonuç odaklı bir karar kılavuzu sağlıyor.

Anahtar kelimeler: Beyin metastazı, makina öğrenmesi, prognoz, radyoterapi, sağkalım.

Address for Correspondence: Emine Elif Özkan; Suleyman Demirel University, Department of Radiation Oncology, Isparta, Türkiye E-mail: ozkanelif@yahoo.com
Received: 19.03.2025 Accepted: 10.08.2025

INTRODUCTION

About 24%–45% of all cancer patients develop brain metastases (BM) in their course [1, 2]. Overall survival (OS) for these patients after palliative whole-brain radiation therapy (WBRT) was reported to be only 4–7 months[3]. Lung, breast, melanoma, and renal cancer are the most common primaries reported with brain metastasis[2,4]. The actual standard of care for brain metastasis includes whole-brain radiotherapy (WBRT), stereotactic radiosurgery, surgery, or any combination of these three modalities performed according to patient and tumor-related factors[1,2]. However, it is a controversial issue whether or not to offer WBRT for all patients, including adverse prognostic factors[5]. As the survival of this subgroup of patients may be limited to even weeks, best supportive care (BSC) is a more rational option. On the contrary, WBRT with lower fraction doses seems to be the appropriate option for patients with an expected survival of more than 6 months due to the longer duration of intracranial control and less late toxicity[6,7]. In order to guide individual decision-making, plenty of prognostic systems and prognostic indices have been suggested. Common indices suggested for the prediction of clinical prognosis in patients with BM included Recursive Partitioning Analysis (RPA), Graded Prognostic Assessment (GPA), and Score Index for Radiosurgery (SIR). Diagnosis-specific GPA (DS-GPA) is an extended version of GPA, including diagnosis-specific information[8]. As all these abovementioned studies are thought to be affected by some selection biases. Rades et al proposed a new scoring tool (WBRT-30) to reduce the bias risk due to the treatment regimen[9].

Although there are different treatment options, such as SRS, tyrosine kinase inhibitors (TKIs), or whole-brain radiation therapy for patients with neurologically symptomatic brain metastases, there are no guidelines in terms of treatment modality selection or follow-up. The appropriate treatment decision for these lesions needs a multidisciplinary team guided by patient characteristics, disease profile, and clinical features. However, most studies to date were not able to stratify their patients based on neurologic symptomatic status, which leads to inappropriate prognostic prediction and inevitable indecision in treatment. Since artificial intelligence technology has been introduced to clinical medicine [10-12], many papers have reported the utilization of machine learning to predict the prognosis of various cancers[13,14]. Machine learning is reported to be superior to conventional statistical methods in forming indices for prognostic prediction in terms of accuracy, sensitivity, and specificity. Previous studies stated that the AI method can be used as a feasible and convenient application to search for an optimal prognosis index for BM patients in clinical use is possible[13,14], however; evidence of their relevance in BM prognosis is scarce[15].

In this study, we aimed to develop an accurate predictive model for the prognosis of patients with brain metastasis and validate it for the estimation of individualized outcome results, which would turn out to be a tool for individualization of treatment strategy for each patient. This predictive model will guide the clinicians to select the accurate treatment modality, which has a spectrum from SRS to best supportive care according to predicted prognosis.

MATERIALS AND METHODS

Sample

The data of 345 patients with brain metastasis who were treated with 30 Gy in 10 fractions of WBRT between 2011 and 2020 were retrospectively analyzed. In this cohort, a total of 15 clinical / laboratory factors are investigated in terms of associations with survival. According to power analysis with effect size (d =0,18), 5% error probability (α = 0.05), %95 power (1-β = 0.95) (correlation: Point biserial model), the needed sample size for the correlation analysis was found to be 325. Taking probable data loss into consideration, 5% added to the sample, and as a result, 345 files were analysed.

In retrospective analysis, 385 patients were evaluated. According to the exclusion criteria (patients who did not complete treatment, under age 18, over age 80, and patients with multiple primary tumors), 345 patients were enrolled in the study.

Radiotherapy

WBRT was given to patients who did not have previous cranial radiotherapy. An individual thermoplastic mask was used to ensure head fixation. WBRT treatment was planned with a 3 mm slice thickness cranial CT. Target volume included the whole brain with the skull base and lamina cribrosa. A total dose of 30 Gy was given via a 6 MV photon using a linear accelerator (VARIAN DBX) with 3 Gy daily on a schedule of five fractions per week. None of the patients received chemotherapy with WBRT. During radiotherapy, dexamethasone 2 mg/day was given to all patients, which was tapered off by half in a week.

Data collection

The study was approved by the Scientific Research Ethics Committee of the Suleyman Demirel University (2023, 17/249). All procedures were performed in terms of the ethical standards of the institutional research committee in alliance with the 1964 Helsinki Declaration and its later amendments. Informed consent was waived owing to the retrospective nature of the study.

After the institutional review board approval, data of patients who underwent palliative WBRT for brain metastasis in Suleyman Demirel University Radiation Oncology Department were collected from electronic files and daily reports from clinical files from the Radiation Oncology Department archive retrospectively. Data were seen and recorded by the authors only.

Data handling and machine learning analysis

In order to determine suitable models, Python 3.11 (Jupyter Notebook, Pycaret Library) was used for data processing and machine learning analysis. PyCaret simplifies processes such as analyzing datasets, automating preprocessing steps, conducting feature engineering, and automatically adjusting model settings, making the modeling process easier and faster. A significant advantage of PyCaret is also its capacity to seamlessly integrate multiple machine learning libraries. Within PyCaret, it can be effortlessly utilized to run algorithms from scikit-learn and many other libraries without switching environments or writing intricate code (www.pycaret.org). Categorical variables are automatically converted into numeric formats using methods such as one-hot encoding, ordinal encoding, and others. Data normalization was performed before model development. The data sets were randomly divided into training and independent testing sets. To avoid overfitting, 5-fold cross-validation was performed during training. All of the evaluation metrics were cross-validated results based on the training set (70%). Performance visualization for a machine learning understanding of model performance, it was evaluated with the plots of the ROC curve, confusion matrix, and classification report. The Kolmogorov–Smirnov test was used to determine if variables are normally distributed.

Overall, 19 machine learning (ML) algorithms were used. MAE (Mean Absolute Error), RMSE (Root Mean Squared Error), R2 (R-squared Score), RMSLE (Root Mean Squared Log Error; a loss function for an image-to-image regression and MAPE (Mean Absolute Percentage Error) were used to compare algorithms. The best model was selected as Gradient Boosting.

One final check by predicting the test/hold-out set and reviewing the evaluation metrics for extra validation was done. This is because the finalized model has been trained on the complete dataset, including the test/hold-out set. The best model was tuned and finalized.

RESULTS

Median age was 62 (28 – 88) years. The primary disease was lung cancer in the majority of patients (43,2%). Most of the cohort were metastatic at presentation, KPS $\geq$ 70, had multiple brain metastases, and had a DS-GPA score of 1 –2.5. The epidemiologic and biochemical features of the patients are given in Table 1.

While the surgery was performed in a minority of the group, the effect of surgery was not tested in the models. The survival rates at 1, 3, 6, and 12 months for the whole series were 75.6, 49.7, 31, and 17.2%, respectively. Median overall survival was 3 (2.33-3.59) months. Clinical features of the whole cohort are given in Table 1

According to our results, survival after brain metastasis was significantly higher for patients who had brain metastasis more than 14.96 months after diagnosis (p:0.001) and patients with breast cancer (p:0.009). Figure 1, 2.

Table 1. Epidemiologic and biochemical features of the whole cohort

Variables		**n (%)**
Gender	female	94 (27.2)
	male	251 (72.8)
Age	mean (SD.)	min - q1 - q2 - q3 - max
	61.3 (10.9)	28 - 55 - 62 - 69 - 88
BMI	25.7 (5.6)	15.2 - 21.6 - 24.8 - 28.7 - 55.8
HB	12.5 (1.9)	5.1 - 11.3 - 12.4 - 13.8 - 17.3
PLT	271.6 (114.9)	10 - 200 - 247 - 317 - 801
ALB	3.6 (0.6)	1.5 - 3.2 - 3.6 - 4 - 4.8
LDH	351.9 (314.4)	112.3 - 212 - 266 - 366 - 2.815
CRP	39.6 (51.7)	0.6 - 4.3 - 16.7 - 54.7 - 311
		n (%)
Number of Brain Lesions	Single	108 (31.3)
	2-4	123 (35.7)
	5 or more	109 (31.6)
	Leptomeningeal	5 (1.4)
Extracranial Metastasis	No	93 (27)
	Yes	252 (73)
Stage IV at Presentation	No	128 (37.1)
	Yes	217 (62.9)
Total LABBM Score	0-1	85 (24.6)
	1.5-2	139 (40.3)
	2.5-3.5	121 (35.1)
Total DSG PA Score	0-1	101 (29.3)
	1.5-2	185 (53.6)
	2.5-3	59 (17.1)
Primer	NSCLC ADENO	90 (26.1)
	NSCLC NONADENO	59 (17.1)
	SCLC	56 (16.2)
	Breast	51 (14.8)
	Melanoma	15 (4.3)
	Colorectal	15 (4.3)
	Unknown Primary	10 (2.9)
	Rcc	10 (2.9)
	Gynecologic	8 (2.3)
	Bladder	8 (2.3)
	Stomach	6 (1.7)
	Prostate	5 (1.4)
	Lymphoma	3 (0.9)
	Sarcoma	2 (0.6)
	Nonmelanoma Skin	1 (0.3)
	Other	6 (1.7)

SD.: Standard deviatoin, q1: percentile 25, q2: percentile 50, q3: percentile 75BMI: Body Mass Index, HB: Hemoglobin, PLT: Platelet, ALB: Albumin, LDH: Lactate dehydrogenase, CRP: C Reactive protein

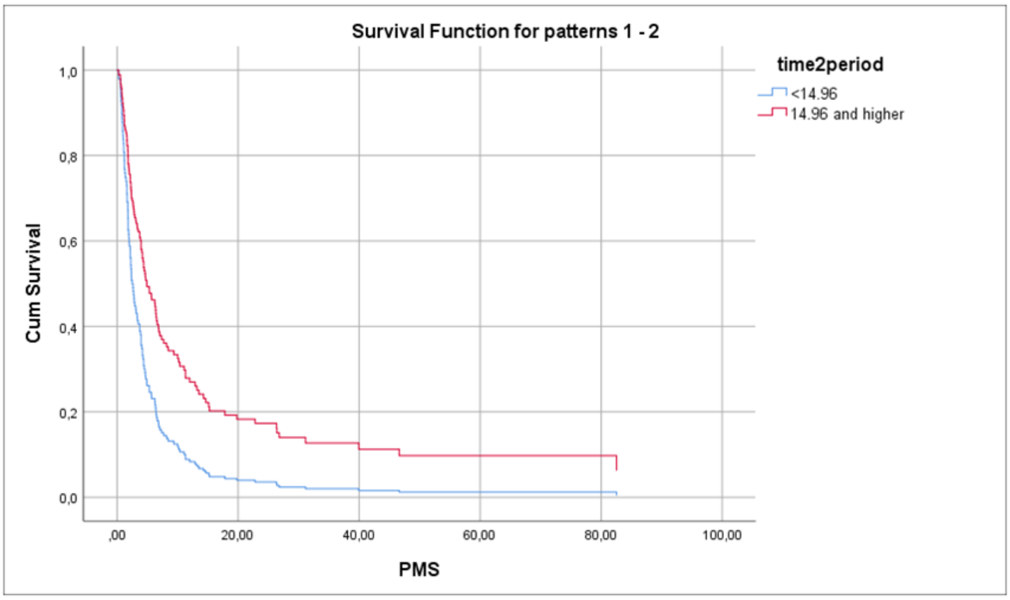

Figure 1. Cumulative survival curve of two group of patients formed according to time from diagnosis to metastasis (months)

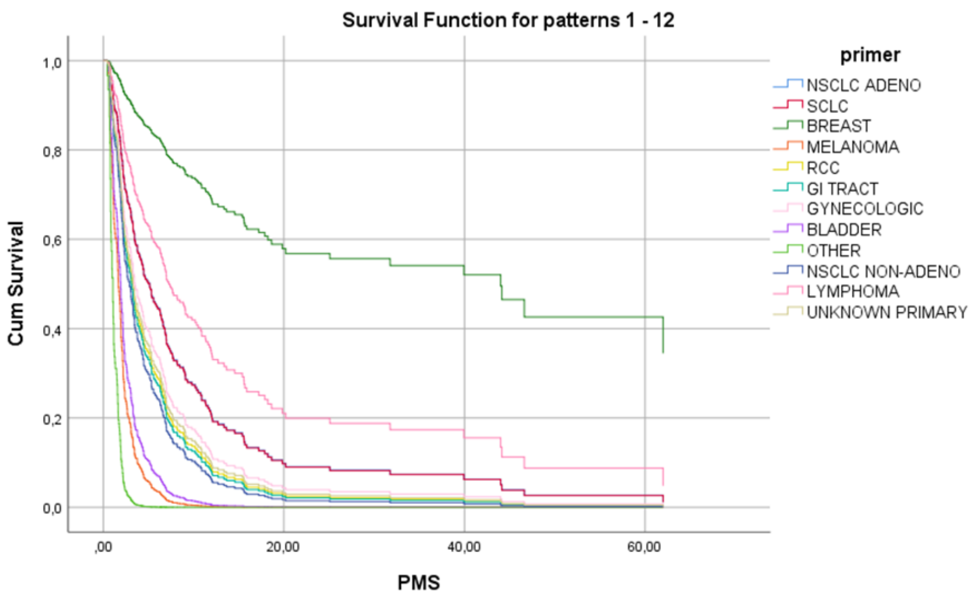

Figure 2. Cumulative survival curve according to primary diagnosis.

After evaluation of 19 models via Python 2.3 Software and Pycaret library, Gradient Boosting Regressor was found to be the accurate modeling with a 0.68 R2 value and 12.90 mean absolute error (MAE) (Table 2). Prediction error for the Gradient Boosting Regressor was calculated as R2: 0.841, and the diagram is plotted in Figure 3.

Table 2. Evaluation of 19 models via Python 2.3 Software, Pycaret library

	Model	MAE	MSE	RMSE	R2	RMSLE	MAPE	TT (Sec)
gbr	Gradient Boosting Regressor	12.9062	8259.9393	49.2551	0.6842	0.6823	0.9515	0.0600
rf	Random Forest Regressor	13.2545	8276.1748	50.1872	0.6628	0.6799	0.9167	0.0920
et	Extra Trees Regressor	13.6878	8327.5408	51.2969	0.6323	0.6990	0.9306	0.0800
ada	AdaBoost Regressor	16.5786	8240.9031	51.7758	0.6209	0.9358	2.0354	0.0520
dt	Decision Tree Regressor	15.7895	8410.5834	52.7919	0.5950	0.8124	1.1334	0.0380
catboost	CatBoost Regressor	14.3300	8356.1049	53.1932	0.5902	0.7512	1.1647	0.5560
knn	K Neighbors Regressor	20.5513	8842.1564	62.9105	0.1848	0.9460	1.4218	0.0420
dummy	Dummy Regressor	28.5079	8883.5506	66.2728	-0.0408	1.3137	3.9995	0.0360
lightgbm	Light Gradient Boosting Machine	27.9306	9720.7779	74.2731	-0.8887	1.1816	2.8224	0.0580
en	Elastic Net	513.4422	60732980.3319	3506.8130	-1542.1457	0.9849	2.3436	0.0320
par	Passive Aggressive Regressor	875.0079	180369357.6326	6030.4927	-4581.0322	1.0298	2.3324	0.0360
br	Bayesian Ridge	873.5898	180699353.1763	6033.0821	-4589.2576	0.9790	2.1790	0.0360
lasso	Lasso Regression	888.6697	187612724.7680	6146.4354	-4764.8262	0.9024	1.9887	0.0320
llar	Lasso Least Angle Regression	888.6712	187613282.8033	6146.4442	-4764.8403	0.9023	1.9888	0.0340
ridge	Ridge Regression	899.5243	191765006.8205	6214.4366	-4870.3238	0.9819	2.2001	0.0400
huber	Huber Regressor	909.9231	196986418.8815	6298.2902	-5002.9499	0.8857	1.7117	0.0360
omp	Orthogonal Matching Pursuit	945.5576	212531537.6479	6541.2099	-5397.7980	0.8968	2.0948	0.0400
lar	Least Angle Regression	5676499150.4749	7894544904904377368576.0000	39735487700.1404	-200519712741204832.0000	1.5572	103271025.7006	0.0380
lr	Linear Regression	235691352262.5878	4742646074737968537403392.0000	1374399910435.8228	-1798723639773497917440.0000	2.5553	64727101759.8080	0.0340

MAE (Mean Absolute Error): A measurement of the typical absolute discrepancies between a dataset's actual values and projected values.
MSE (Mean Squared Error): It measures the square root of the average discrepancies between a dataset's actual values and projected values. It is frequently utilized in regression issues.
RMSE (Root Mean Squared Error): A metric used in regression analysis and machine learning to measure the accuracy or goodness of fit of a predictive model, especially when the predictions are continuous numerical values.
R2 (R-squared Score): A statistical metric frequently used to assess the goodness of fit of a regression model which is also coefficient of determination. R2 is useful for evaluating the overall effectiveness and explanatory power of a regression model.
RMSLE: Root Mean Squared Log Error; a loss function for an image-to-image regression
MAPE: Mean Absolute Percentage Error; a simple average of absolute percentage errors

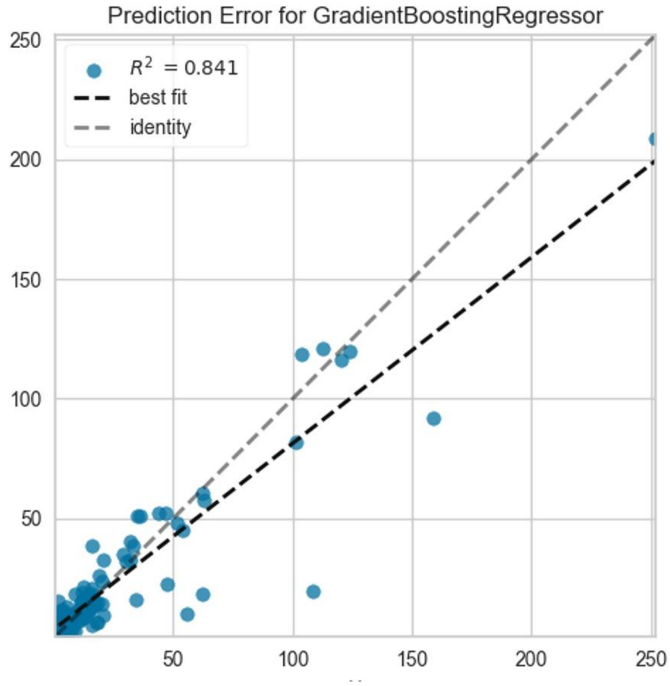

Figure 3. Diagram for prediction error for gradient Boosting Regressor (calculated as R2: 0.841).

When the importance of features was investigated, time from diagnosis to metastasis was found to be the most important predictive variable for survival. The features analyzed were plotted in Figure 4 Kaplan Meier results of the two genders are given in Figure 5.

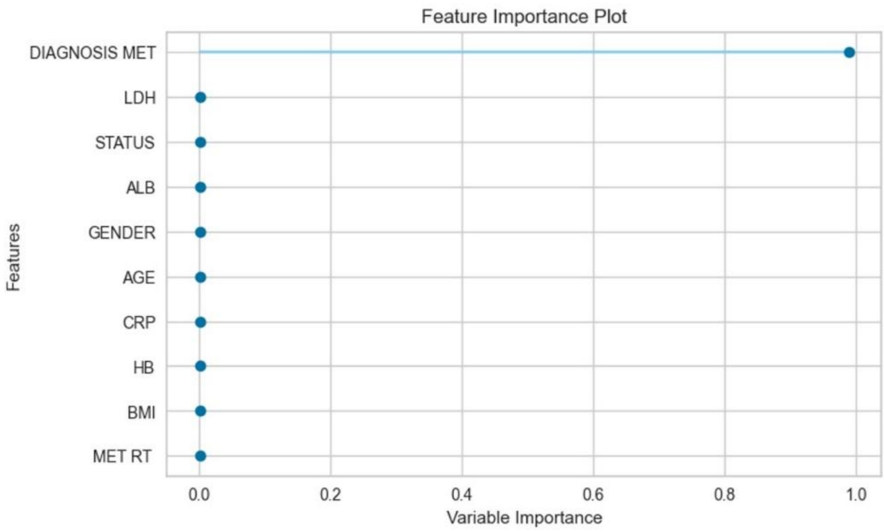

Figure 4. The features analyzed via machine learning algorithm.

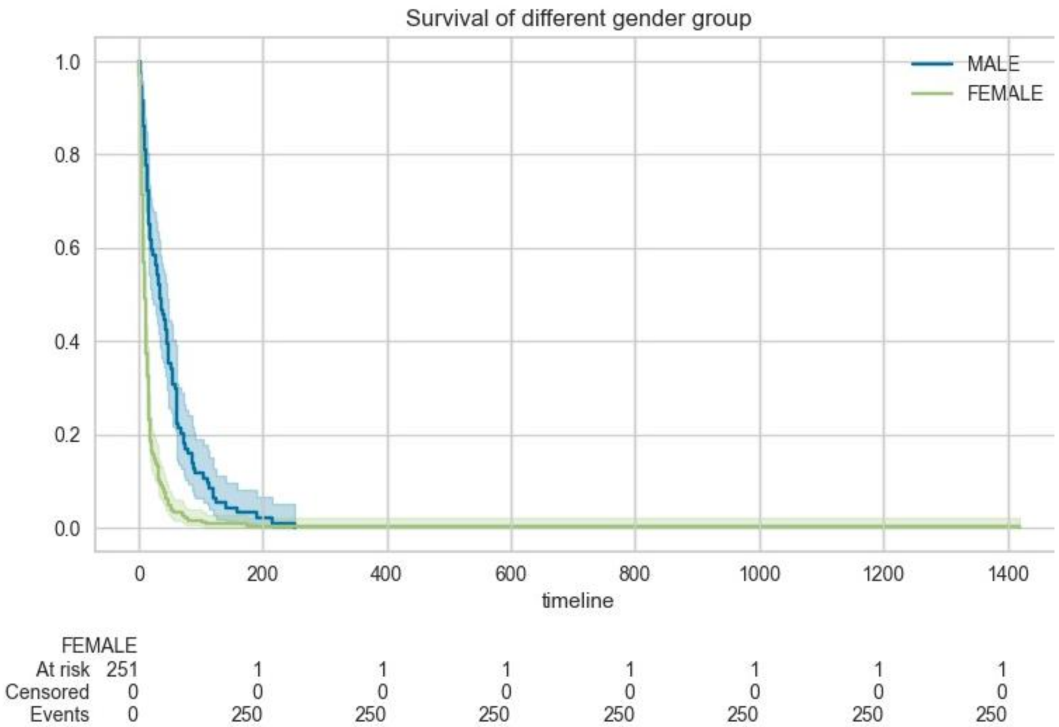

Figure 5. Kaplan Meier results of two genders.

DISCUSSION

Brain metastasis has a significant impact on the prognosis and quality of life of cancer patients. WBI alone is the most common treatment of choice to provide improvement in neurologic dysfunction and prolong life span, resulting in a median survival reported as < 6 months for such patients in previous series[16,17]. The expected median survival for a patient with brain metastases is about 1 month if left untreated[18]. These patients mostly receive radiotherapy, either as WBI alone, local approach (stereotactic radiosurgery or fractionated stereotactic radiotherapy) alone, or as a combination of whole brain and local radiotherapy[19,20]. Despite the increasing utilization of local therapies in clinical practice, WBI alone is still the most common radiotherapy choice for intracerebral metastases. WBI can be administered in different dose-fractionation schedules with short courses (e.g., 5 × 4 Gy over 1 week) or longer courses (e.g., 10 × 3 Gy over 2 weeks and 20 × 2 Gy over 4 weeks)[21]. Preventing clinical status from getting worse with further symptoms, palliation of neurological symptoms, improvement of quality of life (QOL), and increasing overall survival are the major objectives for these patients. The most widely utilized and earliest validated tool is the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA), classifying patients with brain metastases into three prognostic groups[22,23]. According to RPA, the worst prognostic group (class III) has a median survival of 2–2.3 months and was determined solely based on performance status (KPS < 70). Thus, the RPA system was inadequate for identifying patients with a high likelihood of 'early death'[21,24]. Thereafter, additional models including different variables have been proposed to predict survival in patients with brain metastasis. The graded prognostic assessment (GPA), developed by RTOG[25], aimed to decrease subjectivity but still had insufficiencies.

In their previous review, Nieder and Mehta examined the strengths and weaknesses of 6 different prognostic indices, published between 1997 and 2008. These were RPA derived from 3 prospective Radiation Therapy Oncology Group (RTOG) trials, Rotterdam single institutional study, Score Index for Radiosurgery (SIR), a single institution report, Basic Score for Brain Metastases (BSBM), another single institution proposal, GPA derived from 5 prospective RTOG studies, and the prognostic index suggested by Rades et al, with a multi-institutional study[26]. The authors concluded that GPA is the least subjective, most quantitative, and easiest to use of the 4 indices; however, they noted that future trials comparing these scores are warranted to validate the GPA.

However, Buecker et al reported that 18% of patients who were recommended WBI experienced an 'early death'[27] which was in line with the study of Bezjak et al. where 17% of patients died within 4 weeks of WBI and probably had no time to acquire the benefit of treatment[28]. Thus, identifying the subgroup of patients with relatively poor prognosis who are likely to experience an 'early death' at the time of diagnosis may direct the individual management algorithm to steroid therapy and BSC, which may be more suitable for the patient[29]. Thus, nomograms may be more effective for estimating prognosis[30] or disease control[31] for individualized treatment planning rather than 3- or 4-tiered scores. The previous studies evaluated age, extracranial disease, number of brain metastases, performance status (ECOG, KPS), primary site, and histologic subtype in these nomograms[32-37]. To our knowledge, this is the only study including the LabBM score in an attempt to find a predictive model.

Taking the progressive utilization of artificial intelligence, in this study, we aimed to evaluate the potential risk factors in terms of survival in patients with brain metastasis via machine learning strategies to determine who may not benefit from WBI while they are likely to experience ‘early death’.

Huang et al sought the optimum prognosis index for brain metastases by machine learning. Seven features and seven prediction methods were selected in their study to evaluate the prognosis for each patient. The prediction of prognosis was investigated via mutual information and a rough set with particle swarm optimization (MIRSPSO) methods. The authors concluded that identifying optimal machine-learning methods for prognostic prediction in brain metastases was essential for clinical applications, and they stated that the accuracy rate of machine-learning was significantly higher than conventional statistical methods[38].

Artificial neural networks (ANNs) have been suggested as an accurate tool for analyzing challenging data sets and decision support in clinical environments in the last decade. Particularly in neuro-oncology patients, ANNs perform better than traditional statistical tools and scoring indexes for predicting individual patient prognosis. The advantage of robustness in the presence of missing data makes them excellent choices for use in complicated situations[39].

In their meta-analysis, Habibi et al reviewed 17 articles to investigate the accuracy of machine learning (ML) in predicting treatment response and local failure of brain metastasis treated with stereotactic radiosurgery (SRS). The sensitivity and specificity of ML algorithms for predicting treatment response were 0.89 (95% CI: 0.84–0.93) and 0.87 (95% CI: 0.81–0.92), respectively. Sensitivity and specificity for predicting local failure were 0.93 (95% CI: 0.76–0.98) and 0.80 (95% CI: 0.53–0.94), respectively. The authors stated ML as a promising tool in predicting treatment response and local failure in brain metastasis patients receiving SRS[40].

In a recent study, 4 different machine learning (ML) algorithms were used to create prediction models for BMs in ES-SCLC patients. The accuracy, sensitivity, and specificity were compared among these models and traditional logistic regression (LR). The random forest (RF) model demonstrated the best performance and was chosen for further analysis. The authors developed and validated a predictive RF model using clinical and pathological variables to predict the risk of brain metastasis in extensive-stage small-cell lung cancer patients. Conclusively, the authors suggested this model as an assisting tool in making clinical decisions[41].

Using the data and results in our study, we also developed a web application which is available from https://huggingface.co/spaces/Ragio/brainmet/upload/main

There are several limitations to be mentioned. First, due to the retrospective nature of the data, the effect of some factors on the results is inevitable, such as missing variables (eg, comorbidities), and potential selection biases. Second, information regarding metastasectomy was not evaluated due to the small number of patients. Third, details about systemic therapy were lacking. The last limitation we can mention is that the model lacks validation on an external or prospective dataset, which would provide generalizability of our results. Despite these limitations, the present study is an attempt to develop a decision guide via artificial intelligence algorithms to identify the patients who may not benefit from WBI objectively.

With the technical and planning developments in radiotherapy (IMRT, SRS, hippocampal avoidance) and adding effective supportive and symptomatic treatment, longer overall survival will be achieved in a considerable number of patients after WBRT (especially patients with breast cancer[42]. Expected long-term side effects of WBRT, such as impairment of cognitive functions due to damage of neuronal stem cells via ionizing radiation, may be mitigated by hippocampal avoidance and supportive systemic treatments[43,44].

According to the above-mentioned studies and our results, the most appropriate candidates for WBRT are patients with breast cancer who have had brain metastasis for more than 14.96 months after diagnosis. Taking into account an increasing number of patients with brain metastases, this study with a web-based application support will help as a guide for clinicians to make decisions for these patients in terms of only WBRT, WBRT with hippocampal avoidance, adding radiosurgery to WBRT, or even only best supportive care.

The results of this study enable us to identify patients who may have an early death and provide a consequential decision guide in terms of whole-brain radiotherapy or additional labor-intensive techniques such as hippocampal avoidance.

Author Contributions: Concept/Design : EEÖ; Data acquisition: EEÖ; Data analysis and interpretation: -; Drafting manuscript: EEÖ; Critical revision of manuscript: -; Final approval and accountability: EEÖ, TAS; Technical or material support: -; Supervision: -; Securing funding (if available): n/a.
Ethical Approval: The study was approved by the Scientific Research Ethics Committee of the Suleyman Demirel University (2023, 17/249).
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. Oncologist. 2007;12:884–98.
2. Sacks P, Rahman M. Epidemiology of brain metastases. Neurosurg Clin N Am. 2020;31:481-88.
3. Hirose T, Deguchi S, Yasui K, Inoue M, Onoe T, Ogawa H et al. The indication of palliative whole-brain radiotherapy for patients with brain metastases: a simple prognostic scoring system in the era of stereotactic radiosurgery. BMC Cancer. 2024;24:940.
4. Cardinal T, Pangal D, Strickland BA, Newton P, Mahmoodifar S, Mason J et al. Anatomical and topographical variations in the distribution of brain metastases based on primary cancer origin and molecular subtypes: a systematic review. Neurooncol Adv. 2021;4:vdab170.
5. Nieder C, Norum J, Dalhaug A, Aandahl G, Pawinski A. Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. Clin Exp Metastasis. 2013;30:723-29.
6. Li Z, Shen D, Zhang J, Zhang J, Yang F, Kong D et al. Relationship between WBRT total dose, intracranial tumor control, and overall survival in NSCLC patients with brain metastases - a single-center retrospective analysis. BMC Cancer. 2019;19:1104.
7. Rades D, Panzner A, Dziggel L, Haatanen T, Lohynska R, Schild SE. Dose-escalation of whole-brain radiotherapy for brain metastasis in patients with a favorable survival prognosis. Cancer. 2012;118:3852-59.
8. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010;77:655-61.
9. Rades D, Dziggel L, Nagy V, Segedin B, Lohynska R, Veninga T et al. A new survival score for patients with brain metastases who received whole-brain radiotherapy (WBRT) alone. Radiother Oncol. 2013;108:123-27.
10. Kennedy, E.D, Simunovic M, Jhaveri K, Kirsch R, Brierley J, Drolet S et al. Safety and feasibility of using magnetic resonance imaging criteria to identify patients with "good prognosis" rectal cancer eligible for primary surgery: The phase 2 nonrandomized QuickSilver clinical trial. JAMA Oncol. 2019;5:961–66.
11. Wilensky, G.R. Bedside c omputer vision-moving artificial intelligence from driver assistance to patient safety. N. Engl.J.Med. 2018;378:1269–71.
12. Hana T, Tanaka S, Nejo T, Takahashi S, Kitagawa Y, Koike T, et al. Mining-Guided machine learning analyses revealed the latest trends in neuro-oncology. Cancers. 2019;11:178.
13. Ferroni P, Zanzotto FM, Riondino S, Scarpato N, Guadagni F, Roselli M. Breast cancer prognosis using a machine learning approach. Cancers. 2019;11:328.
14. Burki TK. Predicting lung cancer prognosis using machine learning. Lancet Oncol. 2016;17:e421.
15. Kourou K, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J. 2015;138:8–17.

16. Lee YW, Cho HJ, Lee WH, Sonntag WE. Whole brain radiation-induced cognitive impairment: pathophysiological mechanisms and therapeutic targets. Biomol Ther (Seoul). 2012;20:357-70.
17. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive sparing during the administration of whole brain radiotherapy and prophylactic cranial irradiation: current concepts and approaches. J Oncol. 2010;2010:198208.
18. Pease NJ, Edwards A, Moss LJ. Effectiveness of whole brain radiotherapy in the treatment of brain metastases: a systematic review. Palliat Med. 2005;19:288–99.
19. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis (es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2012;2:210-225.
20. Rades D, Huttenlocher S, Dziggel L, Khoa MT, Van Thai P, Hornung D et al. A new tool predicting survival after radiosurgery alone for one or two cerebral metastases from lung cancer. Lung. 2015;193:299-302.
21. Rades D, Kieckebusch S, Lohynska R, Veninga T, Stalpers LJ, Dunst J et al. Reduction of overall treatment time in patients irradiated for more than three brain metastases. Int J Radiat Oncol Biol Phys. 2007;69:1509-13.
22. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37:745-51.
23. Videtic GM, Adelstein DJ, Mekhail TM, Rice TW, Stevens GH, Lee SY et al. Validation of the RTOG recursive partitioning analysis (RPA) classification for small-cell lung cancer-only brain metastases. Int J Radiat Oncol Biol Phys. 2007;67:240-43.
24. Rodrigues G, Warner A, Zindler J, Slotman B, Lagerwaard F. A clinical nomogram and recursive partitioning analysis to determine the risk of regional failure after radiosurgery alone for brain metastases. Radiother Oncol. 2014;111:52-8.
25. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70:510–514.
26. Nieder C, Mehta MP. Prognostic indices for brain metastases--usefulness and challenges. Radiat Oncol. 2009;4:10.
27. Buecker R, Hong ZY, Liu XM, Jaenke G, Lu P, Schaefer U. Risk factors to identify patients who may not benefit from whole brain irradiation for brain metastases - a single institution analysis. Radiat Oncol. 2019;14:41.
28. Bezjak A, Adam J, Panzarella T, Levin W, Barton R, Kirkbride P et al. Radiotherapy for brain metastases: defining palliative response. Radiother Oncol. 2001;61:71-76.
29. Moravan MJ, Fecci PE, Anders CK, Clarke JM, Salama AKS, Adamson JD et al.. Current multidisciplinary management of brain metastases. Cancer. 2020;126:1390-1406.
30. Gittleman H, Lim D, Kattan MW, Chakravarti A, Gilbert MR, Lassman AB et al. An independently validated nomogram for individualized estimation of survival among patients with newly diagnosed glioblastoma: NRG Oncology RTOG 0525 and 0825. Neuro Oncol. 2017;19:669-677.
31. Kent MS, Mandrekar SJ, Landreneau R, Nichols F, Foster NR, DiPetrillo TA et al. A Nomogram to predict recurrence and survival of high-risk patients undergoing sublobar resection for lung cancer: an analysis of a multicenter prospective study (ACOSOG Z4032). Ann Thorac Surg. 2016;102:239-46.
32. Barnholtz-Sloan JS, Yu C, Sloan AE, Vengoechea J, Wang M, Dignam JJ et al. A nomogram for individualized estimation of survival among patients with brain metastasis. Neuro Oncol. 2012;14:910-18.
33. Marko NF, Xu Z, Gao T, Kattan MW, Weil RJ. Predicting survival in women with breast cancer and brain metastasis: a nomogram outperforms current survival prediction models. Cancer. 2012;118:3749-57.
34. Ahn HK, Lee S, Park YH, Sohn JH, Jo JC, Ahn JH et al. Prediction of outcomes for patients with brain parenchymal metastases from breast cancer (BC): a new BC-specific prognostic model and a nomogram. Neuro Oncol. 2012;14:1105-13.
35. Pietrantonio F, Aprile G, Rimassa L, Franco P, Lonardi S, Cremolini C, et al. A new nomogram for estimating survival in patients with brain metastases secondary to colorectal cancer. Radiother Oncol. 2015;117:315-21.
36. Ayala-Peacock DN, Attia A, Braunstein SE, Ahluwalia MS, Hepel J, Chung C, et al. Prediction of new brain metastases after radiosurgery: validation and analysis of performance of a multi-institutional nomogram. J Neurooncol. 2017;135:403-11.
37. Zindler JD, Jochems A, Lagerwaard FJ, Beumer R, Troost EGC, Eekers DBP et al. Individualized early death and long-term survival prediction after stereotactic radiosurgery for brain metastases of non-small cell lung cancer: Two externally validated nomograms. Radiother Oncol. 2017;123:189-94.
38. Huang S, Yang J, Fong S, Zhao Q. Mining prognosis index of brain metastases using artificial intelligence. Cancers (Basel). 2019;11:1140.
39. Oermann EK, Kress MA, Collins BT, Collins SP, Morris D, Ahalt SC, et al. Predicting survival in patients with brain metastases treated with radiosurgery using artificial neural networks. Neurosurgery. 2013;72:944-51

40. Habibi MA, Rashidi F, Habibzadeh A, Mehrtabar E, Arshadi MR, Mirjani MS. Prediction of the treatment response and local failure of patients with brain metastasis treated with stereotactic radiosurgery using machine learning: A systematic review and meta-analysis. Neurosurg Rev. 2024;47:199.
41. Munai E, Zeng S, Yuan Z, Yang D, Jiang Y, Wang Q et al. Machine learning-based prediction model for brain metastasis in patients with extensive-stage small cell lung cancer. Sci Rep. 2024;14:28790.
42. Palácová M, Svobod, M, Fabian P, Ondrová B, Grell P, Jana G et al. Tumor phenotype and characteristics of metastatic brain involvement in breast cancer patients: potential clinical consequences, ASCO annual meeting proceedings 2009. J Clin Oncol. 2009;27:1026.
43. Scoccianti S, Detti B, Cipressi S, Iannalfi A, Franzese C, Biti G. Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy. J Neurooncol. 2012;108:291–308.
44. Monje ML, Palmer T. Radiation injury and neurogenesis. Curr Opin Neurol. 2003;16:129–34.