

Glioblastoma cancer: comparing the effectiveness of 3D conformal radiation therapy and volumetric modulated radiotherapy - an artificial intelligence-based survival prediction

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Abstract

This study aimed to evaluate the survival efficacy of different radiotherapy strategies in patients with glioblastoma (GBM). Furthermore, by utilizing various artificial intelligence algorithms and machine learning models, including neural networks, logistic regression, and decision trees, among others, the possibility of

obtaining outcome predictions for a specific point in time was explored.

The study considered data from radiotherapy treatments for patients affected by GBM. Eligible data included patients treated with 3D conformal radiotherapy or intensity-modulated radiotherapy, who reported overall survival and progression-free survival. The impact of different radiotherapy modalities on survival was evaluated through direct comparisons of the available data.

In the second part of the study, the possibility of using artificial intelligence to predict the survival status of patients after a specific period following the end of radiation treatment was explored. To test our hypothesis, we used data from new patients and asked the machine learning models with the best fit to our data to predict survival for these new patients.

A total of 30 elderly GBM patients treated with modern radiotherapy strategies were examined, showing a better overall survival when volumetric modulated radiotherapy (VMAT) was used compared to the 3D conformal radiation therapy technique. The artificial intelligence algorithm was asked to predict the survival status of three new patients. The neural network method, compared to the others used, is the one that responded correctly in 100% of the cases submitted. In second place was the decision tree method, which responded correctly in 67% of the cases.

Our results suggested VMAT as a standard radiotherapy modality with potentially superior survival outcomes for selected patients with GBM.

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Introduction

Glioblastoma (GBM) is a highly composite and aggressive brain tumor, making it the most common type of brain tumor in adults. GBM can arise from any location within the central nervous system, but it primarily occurs in the frontal or temporal lobes.¹⁻⁴ GBM is a diffuse grade IV astrocytoma, a highly malignant subtype with high rates of cell division, high vascularity, and areas of tumor necrosis,^{5,6} and it is a brain tumor associated with a poor prognosis.

In recent years, the entire process related to radiotherapy treatment has improved significantly, keeping pace with technological progress that offers new therapeutic modalities, such as 3D conformal radiation therapy (3D-CRT) or the newer technique called volumetric modulated arc therapy (VMAT), in which the intensity of the incident radiation is modulated, allowing a significant reduction in the dose delivered to the surrounding organs at risk (OAR) while delivering a high dose of radiation to the target volume.^{7,8}

Artificial intelligence (AI) can be defined as the ability of a machine to imitate human intelligence. AI relies on a fundamental characteristic: the ability to learn automatically. Machine learning (ML) can be defined as a mathematical algorithm that learns through experience.⁹

In clinical activities, two key factors in patient treatment are knowledge and experience. The human learning process is constrained by the time needed to gain solid clinical experience and the challenges of managing the growing amounts of data available in the field. This difficulty for humans is instead an advantage for AI: the availability of large amounts of data is essential to train modern computational learning algorithms.^{10,11}

AI that widely uses ML is a set of techniques that automatically learn patterns from data and do not require assumptions about the structure of the data.

Four different ML methods were considered: tree, neural network, naïve Bayes, and logistic regression, which were compared to identify the best fit for our data.

A strength of these techniques is that they can recognize nonlinear relationships in the data, as well as the interaction between features. Many studies have demonstrated their encouraging performance for disease prediction.¹²⁻²¹

This report aims to test the possibility of using AI to predict the survival status of patients after a certain time following radiotherapy treatment, comparing VMAT with the 3D-CRT technique to investigate the overall survival of patients.

Materials and Methods

Patients

The patients examined are all Caucasian individuals in good health before the oncological diagnosis, with no significant risk factors associated with the tumor. Figure 1 shows the distribution of patients by age. During the radiation treatment, they were seen weekly and evaluated from a neurological point of view without evidence of sensory-motor toxicities. About a month after the radiation treatment, a clinical check-up was repeated, which once again

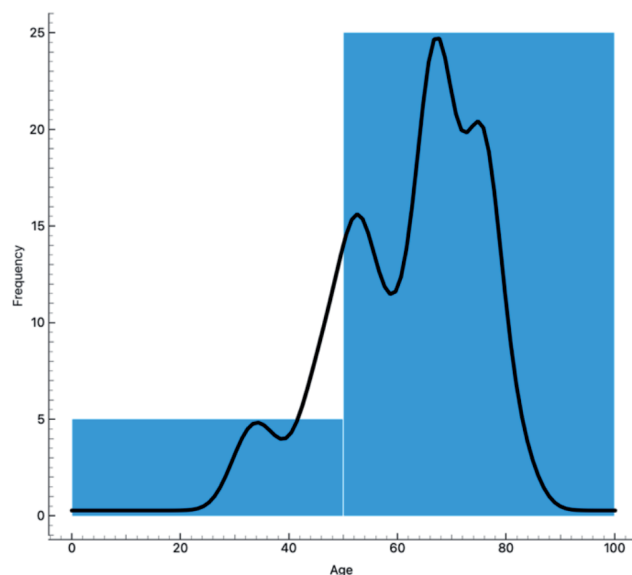


Figure 1. Distribution of patient ages.

showed no side effects. After this check, a clinical and instrumental follow-up with a brain magnetic resonance imaging (MRI) was performed every 4 months.

Radiotherapy treatment

The therapeutic plan was carried out according to the National Comprehensive Cancer Network and European Society for Radiotherapy and Oncology guidelines.^{22,23} Before delineating the treatment volumes, an image fusion procedure was performed between the post-operative computed tomography and follow-up MRI. Contouring was performed on T1-weighted contrast-enhanced and T2-weighted FLAIR MRI sequences to highlight and include cerebral edema. All plans were subsequently processed with Monaco software and carried out on Versa HD Linac (Elekta, Stockholm, Sweden) and Clinac (Varian, Palo Alto, CA, USA) systems.

Treatment

Treatment planning

The GBM dose for most patients was 60 Gy (30 fractions of 2 Gy). Treatment plans based on VMAT were generated for approximately half of the patients, while for a second group of subjects, dosimetric plans were developed with the 3D-CRT technique using coplanar fields.

Dose calculations used inverse planning optimization (Monaco treatment planning system version 5.11.02, Elekta, Stockholm, Sweden) and a Monte Carlo algorithm. The dosimetric physical plan was optimized using biological cost functions: equivalent uniform dose for planning target volume (PTVs) and serial/parallel cost functions for OAR. GBM treatment plans used 6 MV photon energy. In the planning phase, priority was given to target dose coverage and homogeneity; therefore, >95% of the PTV volume was covered by 95% of the prescribed dose, and the maximum dose of the plan did not exceed 107%. Furthermore, the dosimetric plan has been optimized to minimize the OAR dose without altering the target coverage.

Planning target volume dosimetry

PTV coverage (D95%) was adequate for all plans, and the maximum dose is around 107% of the dose prescription for all plans. Figure 2 shows the isodose for both VMAT and 3D-CRT in axial, sagittal, and coronal plans.

Mean PTV dosimetry parameters between the 3D-CRT and VMAT techniques in GBM irradiation can be seen in Table 1. The statistical analyses of PTV dosimetry parameters show agreement with the scientific evidence already described in the literature. Dose conformity index, D98, D50, and Dmean were superior with VMAT in all patients with a statistically significant difference ($p=0.05$), while Dmax, D2, and HI were the same for both VMAT and 3D-CRT plans. In particular, the mean confidence interval (0.32) for 3D-CRT was lower than for VMAT (0.84) and shows the VMAT technique's conformational power.

Table 2 summarizes some absorbed doses from OARs and the p -value of the comparison of dosimetric parameters for the organs present in the table.

Cluster analysis

Data to analyze comes in many forms. A collection of healthcare data may be analyzed primarily to produce new insights. Over the past century, as computers have evolved in speed and capacity, new machine-learning techniques have emerged that allow researchers to uncover hidden patterns beyond what traditional statistical analysis

could provide. One type of ML technique, cluster analysis, classifies and sorts data sets into groups, or clusters, based on a measure of similarity. This method, which shares some commonalities with content analysis, can be used to identify patterns and logical groupings in large data sets that would otherwise be too difficult to analyze manually. One of the most widely used algorithms for cluster analysis is k-means.^{24,25}

Machine learning models

A probabilistic model is a tool that uses current observations to predict a future event. The model relies on the laws of probability distribution to represent all the unobserved uncertain quantities and explain how they relate to the data. Ultimately, the basic rules of probability theory are used to find the unobserved data from the observed data. This method of learning data from probability theory

is called Bayes' rule. It allows *a posteriori* research of the causes of an event that has occurred.^{26,27}

In this study, using various AI algorithms and ML models, including neural networks, logistic regression, naïve Bayes, and decision trees, the possibility of obtaining outcome predictions is explored.

Results and Discussion

We attempted to investigate the relationships within our data by applying multidimensional scaling (MDS), which is one of the multivariate data analysis techniques used to represent high-dimensional data in a lower-dimensional space. More formally, we used MDS to reduce the complexity of the dataset, allowing for the visualization of the underlying relational structures it contains.

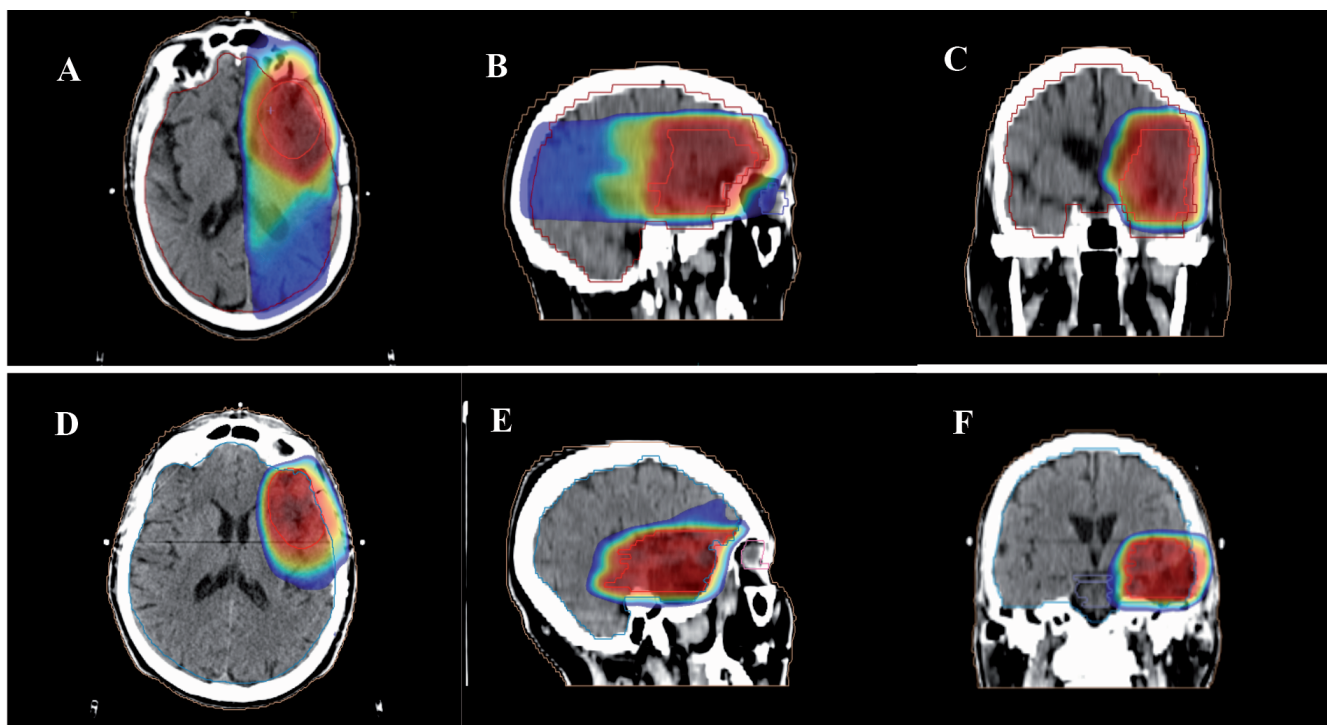


Figure 2. The dose distribution for the 3D conformal radiation therapy plan is organized in three views: axial (A), sagittal (B), and coronal (C); the dose distribution of the volumetric modulated radiotherapy plan is shown in axial (D), sagittal (E), and coronal (F) views.

Table 1. Planning target volume dosimetry parameters value for both 3D conformal radiation therapy and volumetric modulated arc therapy plans, and the relative p-value.

Parameter	3D-CRT		VMAT		p
	Mean	SD	Mean	SD	
D98	55.50	2.81	59.03	1.17	0.041
D50	60.31	0.54	61.14	0.41	0.026
D2	62.13	1.24	62.69	0.26	0.221
Dmean	60.03	0.54	61.07	0.45	0.013
Dmax	63.02	1.39	64.49	0.64	0.063
HI	1.08	0.03	1.05	0.02	0.081
CI	0.32	0.13	0.84	0.03	0.002

3D-CRT, 3D conformal radiation therapy; VMAT, volumetric modulated arc therapy; SD, standard deviation; D98, dose received at 98% of volume; D50, median dose; D2, dose received at 2% of volume; Dmean, mean dose received; Dmax, maximum dose received; HI, heterogeneity index; CI, conformity index.

Figure 3A graphically shows an estimate of the similarity between the elements in our dataset, where the MDS algorithm focused on survival characteristics and the radiotherapy technique used. From this graphical representation, it is easy to observe that the data are essentially divided into two main groups. A few other data points appear completely isolated, which we can define as outliers.

Once the first hidden relationships between the data in our dataset were highlighted using the MDS tool, we continued to analyze them using Cluster analysis methods.

The method used was the K-means algorithm, a simple and fast classical algorithm for solving cluster problems, which uses the parameter k : the number of clusters to calculate. It then divides the dataset into k clusters based on the high similarities within each cluster. After reviewing the results provided by MDS for our analysis, we decided to use k greater than 2. The result of the k -means algorithm is shown in Figure 3B and C.

The graph in Figure 3B shows the survival of patients concerning the radiotherapy technique used. The figure is composed of two images, each corresponding to the two clusters ($k=1$, $k=2$) created by k -means. As already highlighted by the MDS results (Figure 3A), it is clear that there is a cluster populated by a few individuals (Figure 3B on the right) composed of the data most disconnected from the others (outliers).

In Figure 3C, on the other hand, the survival of patients is shown with the dose delivered during the radiotherapy treatment. Again, the image on the right contains the data defined as outliers. We believe that the few cases that showed an anomalous trend should still be investigated to understand the reason. Therefore, these cases will be the subject of further investigation.

Data analysis, shown in Figure 3B and C, demonstrated that survival was superior in the VMAT group. In particular, Figure 3C clearly shows that the patients with the longest survival were those who received the highest therapeutic dose. This leads to a reduced likelihood of developing late side effects or secondary malignancies compared to the 3D technique. VMAT allows for a higher dose to the

target with greater sparing of critical organs compared to 3D-CRT.²⁸

The entire treatment preparation process (from planning to treatment delivery) with VMAT requires more time and, therefore, more valuable resources compared to 3D-CRT.²⁹

The use of the VMAT technique improved compliance and provided the possibility of an increase in the dose to the tumor, minimizing the dose to the OAR compared to 3D-CRT.³⁰ Considering the concept of dose escalation, VMAT, compared to 3D, provides more conformal radiotherapy, with dose escalation in high tumor risk areas and more sparing of critical structures (OAR). In addition to the result just indicated, which is achieved with the VMAT technique, there is a further benefit on the patient's quality of life, for the minimization of treatment-related toxicities compared to 3D-CRT.

Artificial intelligence to predict

Given the previous considerations, in which we saw that some data are to be considered outliers, we revised our dataset by excluding individuals with values defined as anomalous. At this point, we asked ourselves which ML model could best represent the behavior of our dataset. For this purpose, we used four different AI algorithms and trained them using our data: neural network, logistic regression, decision tree, and naïve Bayes.

It was necessary to evaluate which AI model obtained the best fit considering all the predictors of our dataset. For this evaluation, several performance metrics were used, specifically: area under the receiver operating characteristic curve (AUC), classification accuracy, F-score, precision, recall (sensitivity), and Matthews correlation coefficient.

From this comparison, it was seen that the tree and neural network models are the ones that can best represent the data set of this study. In particular, the performance values of the neural network model indicate that this model comprehensively represents our system (100%) our system. Recall that supervised learning neural network algorithms can learn and adapt to dynamic data sets and thus

Table 2. Organ at risk doses and p-values for the most critical organs are shown.

OAR	Right lens		Left lens	
	Dmean (Gy)	Dmax (Gy)	Dmean (Gy)	Dmax (Gy)
3D-CRT	3.84	4.14	5.89	7.10
VMAT	3.41	5.03	3.64	5.76
p	0.447	0.391	0.225	0.330
OAR	Right eye		Left eye	
	Dmean (Gy)	Dmax (Gy)	Dmean (Gy)	Dmax (Gy)
3D-CRT	4.08	5.75	6.58	9.84
VMAT	5.04	10.34	6.31	23.29
p	0.391	0.174	0.467	0.066
OAR	Right optic nerve		Left optic nerve	
	Dmean (Gy)	Dmax (Gy)	Dmean (Gy)	Dmax (Gy)
3D-CRT	5.03	8.48	7.64	12.29
VMAT	8.39	13.13	17.48	33.17
p	0.177	0.197	0.035	0.075
OAR	Brain stem		Optic chiasm	
	Dmean (Gy)	Dmax (Gy)	Dmean (Gy)	Dmax (Gy)
3D-CRT	13.08	46.63	12.48	32.55
VMAT	13.15	43.86	25.65	52.32
p	0.496	0.320	0.020	0.083

OAR, organ at risk; 3D-CRT, 3D conformal radiation therapy; VMAT, volumetric modulated arc therapy; Dmean, mean dose received; Dmax, maximum dose received.

identify complex patterns and models when solving nonlinear problems. Furthermore, the neural network algorithm uses all the available features with a higher complexity, and we attempted to identify how models in their computations. Figure 4A compares the weighted use of the predictors of the AUC performance metric for the tree and neural network models.

In a subsequent analysis, we questioned whether the two identified models (tree, neural network) can predict the clinical outcome of a patient after undergoing radiotherapy. Therefore, we provided both models with input from three additional patients whose survival status is known.

Therefore, we provided as input to the two AI models (tree, neu-

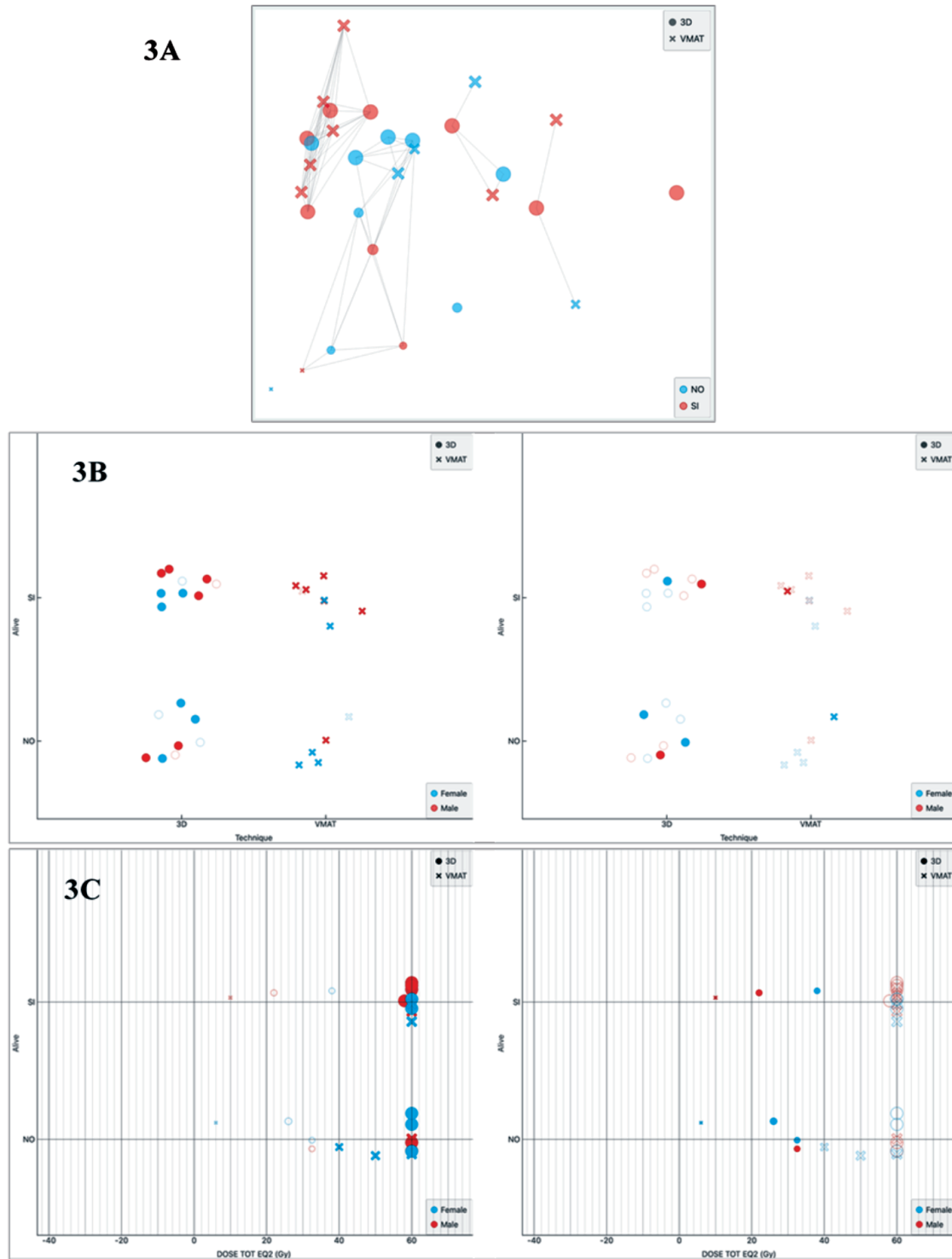


Figure 3. A) The multidimensional scaling tool shows the relationships between the data in our dataset; B) patient survival rates are presented in relation to the radiotherapy techniques used; C) patient survival rates are displayed in relation to the dose delivered. VMAT, volumetric modulated arc therapy.

ral network) three additional patients with all the features present in our data set, except the survival state feature, even if known to us. The alive feature is set as a target, and we ask the two models to process it and predict the survival state.

The tree model correctly answers the patient's survival status twice, or 66.6% of the time, while the neural network algorithm correctly answers three times out of three, or 100% of the cases (Figure 5).

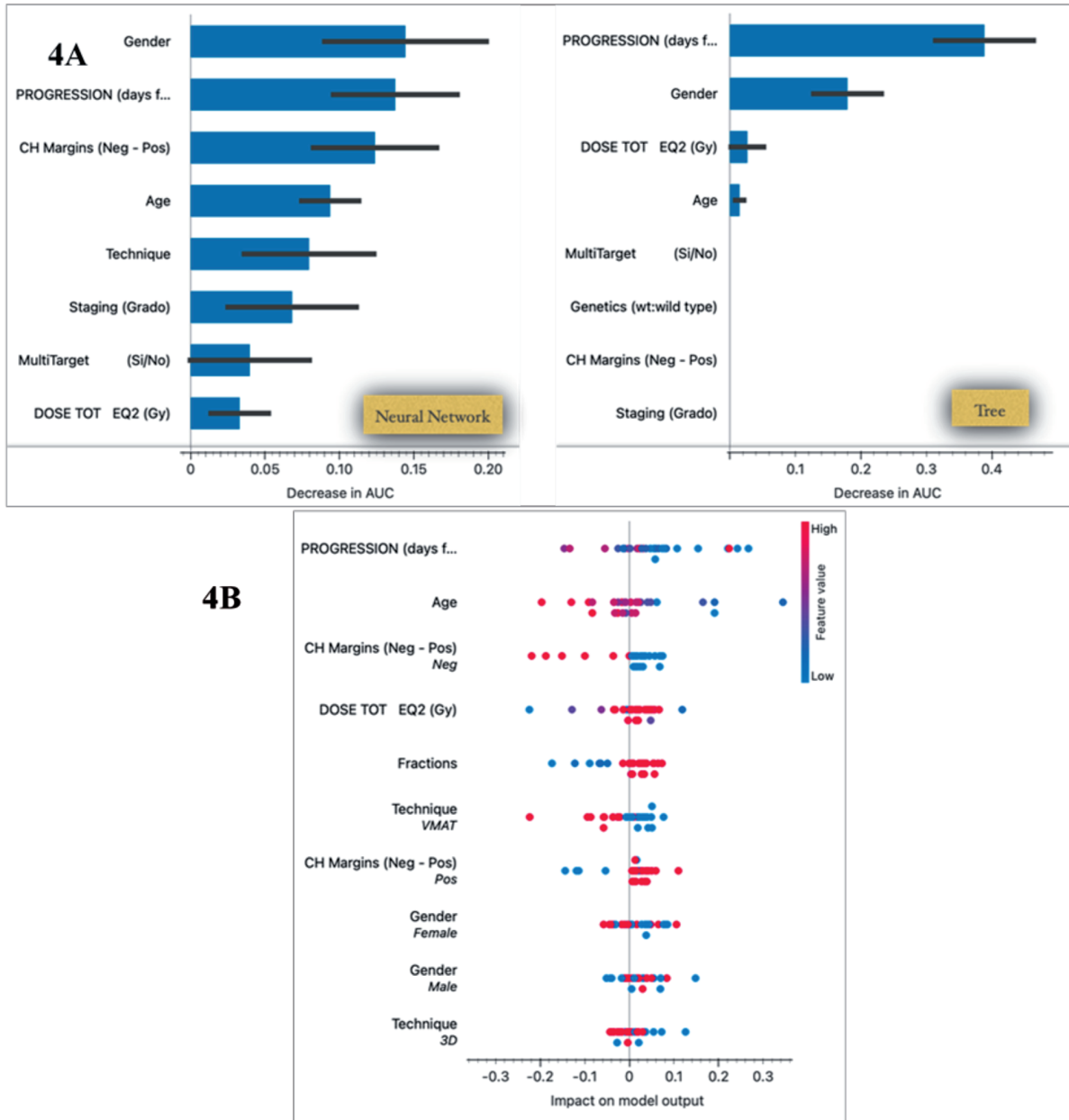


Figure 4. A) Comparison of the weighted use of the predictors of the area under the curve (AUC) performance metric for the tree and neural network models; B) the role of each feature assessed by the Neural Network model on the outcome is illustrated.

	Tree	Neural Network	Alive
1	0.00: 1.00 → Yes	0.96: 0.04 → NO	NO
2	0.00: 1.00 → Yes	0.11: 0.89 → Yes	Yes
3	1.00: 0.00 → NO	0.67: 0.33 → NO	NO

Figure 5. The text in the figure compares the predictions of two artificial intelligence models (tree, neural network) with the actual survival status (alive) of three patients.

Decision trees operate by dichotomies (progression: yes/no, alive: yes/no) and are part of the hierarchical classification or segmentation techniques, to make the segmentation a single variable is selected from all those available. The classification rule obtained through segmentation is used for forecasting purposes. The tree model, as shown in Figure 5, only displays a dichotomous result, either “YES” or “NO” for each patient.

On the contrary, the neural network model has a percentage value as a result. As we can see from Figure 5, the neural network model, for each result, expresses a percentage value associated with YES and a complementary value for NO. If we consider the first row, we have 96% for NO and 4% for YES. The final answer will be linked to the value that has the highest percentage. The neural network algorithm in expressing its result is based on a mechanism that associates a weight and a value to each feature, and the final result will take into account all the features processed (Figure 4B).

Conclusions

Currently, there is no mandatory guidance from scientific societies for the use of a specific radiotherapy technique for GBM, but only suggestions to reduce possible radiation-induced toxicity. In clinical practice, centers that have the VMAT technique prefer to treat most patients affected by GBM with this technique and only some with 3D-CRT.

The use of VMAT for the treatment of GBM is very promising and ensures low doses are delivered to surrounding organs, resulting in a better quality of life for patients undergoing radiotherapy. Our results suggested VMAT as the preferred radiotherapy modality, with potentially superior survival outcomes. Furthermore, this study, although currently based on a limited amount of data, supports the extremely powerful idea that AI methods can be effective tools in supporting accurate predictions of the future clinical development of patients.

In conclusion, we demonstrate that Neural Networks, compared to more commonly used ML models, perform well as an ML model for predicting clinical outcomes in a study of moderate sample size and with a limited set of clinical predictors.

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