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Original article

Application of a multi-institutional nomogram predicting salvage whole brain radiation-free survival to patients treated with postoperative stereotactic radiotherapy for brain metastases

Validation externe d'un nomogramme multi-institutionnelle de prédiction de la radiothérapie encéphalique de sauvetage après irradiation stéréotaxique des métastases cérébrales

A. Mousli[a,b,*], B. Bihin[c,1], T. Gustin[d], G. Koerts[e], M. Mouchamps[f,g], J.-F. Daisne[a,h]

[a] *Radiation oncology department, CHU-UCL-Namur, site Sainte-Elisabeth, université catholique de Louvain, Namur, Belgium*
[b] *Radiation oncology department, Tunis El Manar university, Salah Azaiez Institute, Tunis, Tunisia*
[c] *Biostatistics unit, CHU-UCL-Namur, site Godinne, université catholique de Louvain, Yvoir, Belgium*
[d] *Neurosurgery department, CHU-UCL-Namur, site Godinne, université catholique de Louvain, Yvoir, Belgium*
[e] *Neurosurgery department, centre hospitalier régional Sambre et Meuse, Namur, Belgium*
[f] *Neurosurgery department, centre hospitalier régional de Liège, Liège, Belgium*
[g] *Neurosurgery department, centre hospitalier chrétien Saint-Joseph, Liège, Belgium*
[h] *Radiation oncology department, katholieke universiteit Leuven, university hospitals Leuven, Leuven, Belgium*

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ABSTRACT

Purpose. – The ultimate goal of stereotactic radiotherapy (SRT) of brain metastases (BM) is to avoid or postpone whole brain radiotherapy (WBRT). A nomogram based on multi-institutional data was developed by Gorovets, et al. to estimate the 6 and 12-months WBRT-free survival (WFS). The aim of the current retrospective study was to validate the nomogram in a cohort of postoperative BM patients treated with adjuvant SRT.
Material and methods. – We reviewed the data of 68 patients treated between 2008–2017 with postoperative SRT for BM. The primary endpoint was the WFS. The receiver operating characteristic curve and area under the curve (AUC) were calculated for both 6- and 12-months time points.
Results. – After a median follow-up of 64 months, the 1-year cumulative incidence of local and distant brain relapse rates were 15% [95% CI = 8–26%] and 34% [95% CI = 24–48%], respectively. At recurrence, repeated SRT or salvage WBRT were applied in 33% and 57% cases, respectively. The WFS rates at 6 and 12 months were 88% [95% CI = 81–97%] and 67% [95% CI = 56–81%], respectively. Using the Gorovets nomogram, the 6 months rates were overestimated while they were accurate at 12 months. AUC values were 0.47 and 0.62 for the 6- and 12-months respectively. Overall, Harrell's concordance index was 0.54.
Conclusion. – This nomogram-predicted well the 12 months WFS but its discriminative power was quite low. This underlines the limits of this kind of predictive tool and leads us to consider the use of big data analysis in the future.

Mots clés :
Métastases cérébrales
Nomogramme

RÉSUMÉ

Objectif de l'étude. – La validation externe du nomogramme de Gorovets et al. de l'estimation de la survie sans recours à l'irradiation encéphalique totale de sauvetage après radiothérapie stéréotaxique des métastases cérébrales (basé sur des données multi-institutionnelles).

* Corresponding author at: Radiation oncology department, CHU-UCL-Namur, site Sainte-Elisabeth, université catholique de Louvain, Namur, Belgium.
E-mail addresses: alia_1709@live.fr (A. Mousli), benoit.bihin@uclouvain.be (B. Bihin).
[1] Author responsible for statistical analysis.

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Facteurs prédictifs
Radiothérapie stéréotaxique

Matériel et méthodes. – Cette cohorte porte sur 68 patients traités entre 2008–2017 par une irradiation stéréotaxique pour des métastases cérébrales opérées. Le critère d'évaluation principal était l'irradiation encéphalique totale de sauvetage. Les courbes ROC (« Receiver operating characteristic ») et AUC (« Area under curve ») ont été calculées à 6 et 12 mois.

Résultats. – Après un suivi médian de 64 mois, l'incidence cumulée des taux de rechutes cérébrales locales et à distantes étaient respectivement de 15 % [IC 95 % (intervalle de confiance à 95 %) = 8–26 %] et de 34 % [IC 95 % = 24–48 %] à 12 mois. Au moment de la première récidive, une deuxième radiothérapie stéréotaxique a été indiquée dans 33 % des cas et une irradiation de l'encéphale en totalité de sauvetage dans 57 %. Les taux d'irradiation encéphalique totale de sauvetage à 6 et 12 mois étaient respectivement de 88 % [IC 95 % = 81–97 %] et 67 % [IC 95 % = 56–81 %]. En se référant au nomogramme de prédiction de Gorovets et al., la radiothérapie encéphalique totale de sauvetage était légèrement surestimée à 6 mois alors qu'elle concordait parfaitement à 12 mois. Les valeurs d'AUC étaient respectivement de 0,47 et 0,62 à 6 et 12 mois. L'indice de concordance de Harrell était de 0,54.

Conclusion. – Ce nomogramme permet de prédire le recours à l'irradiation de l'encéphale en totalité de sauvetage à 12 mois. Cependant, la puissance discriminative du nomogramme reste faible, soulignant l'importance de l'analyse à travers des « Big Data » dans l'avenir.

1. Introduction

Stereotactic radiosurgery (SRS) or stereotactic fractionated radiotherapy (SRT) is established treatment options for newly diagnosed, untreated brain metastases (BM) as well as for postoperative cavities [1–3]. SRS and SRT provide a 1-year-local control (LC) rate of 65–90% regardless of histology, as shown in prospective and retrospective studies [1,2,4,5], at the cost of a higher risk of distant brain relapse (DBR) in comparison to whole brain radiotherapy (WBRT). Novel systemic agents like targeted therapies and immune check point inhibitors (ICI) have recently improved the survival prognosis of some metastatic cancers [6], increasing the relative risk of a delayed local relapse (LR) or DBR after SRS/SRT on the long term [7].

The optimal treatment of recurrent/new BM remains unclear because of the lack of high-level evidence [7]. WBRT, repeated SRS/SRT or surgery are commonly used as salvage treatments. Repeated SRS/SRT is a viable alternative because it is less invasive than surgery and it reduces the risk of neurocognitive and quality of life deterioration compared to WBRT [5]. The question of salvage treatment after SRS/SRT failure was addressed in four small heterogeneous and retrospective cohort studies in which multiple courses of SRS/SRT seem to be a safe and effective approach [5].

Since the ultimate goal of first line or repeated SRT is to avoid or delay the WBRT and its cognitive side effects, an objective selection of the patients for the right technique is key. A nomogram predicting the WBRT-free survival (WFS) was developed on a retrospective cohort of 895 patients with a performance status 0–1 and treated in two academic centers with SRS for up to five newly diagnosed < 4 cm BM [8]. Eleven percent received SRS on postoperative cavities. In case of relapse, repeat SRS was applied if the same clinical criteria applied, otherwise WBRT was prescribed. Significant independent predictors for inferior WFS were age, HER-2 (−) breast cancer, colorectal cancer, increasing number of BM, neurologic symptoms, progressive systemic disease and increasing extracranial disease burden. The concordance index was 0.62. The model is based on clinical factors easy to obtain during the first consultation, when a treatment choice has to be operated. Anyway, an external validation is warranted.

We performed a single center, retrospective study of the patients treated with postoperative SRS/SRT after resection of at least one BM at initial diagnosis. The goal is to provide an external validation of the "Gorovets" nomogram with this selected population. Overall survival (OS), LR, DBR, retreatment patterns and WFS were also analyzed.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the data of the 68 patients treated in our center between April 2008 and July 2017 with postoperative SRS/SRT for BM without upfront WBRT for whom sufficient follow-up data were available (>6 months). Surgical resection was performed to palliate neurological dysfunctions or intracranial pressure. Selection criteria for postoperative SRS/SRT were a number of BM (including the resected ones) ≤ 3, a resection cavity size ≤ 5 cm and recursive partitioning analysis (RPA) class I or II. In order to validate the Gorovets nomogram, we collected the same clinico-pathological variables, i.e. age at time of SRT, primary histology (indicator variables: non-small cell lung cancer; HER-2-positive breast cancer; HER-2-negative breast cancer; colorectal cancer; melanoma; other), number of BM treated (1; 2; 3), presence of any neurological symptoms (present; absent), systemic disease status (stable; progressive), and extracranial disease burden (none; oligometastatic ≤ 5; widespread > 5). Patients who were treated at the time of their initial cancer diagnosis were considered in stable disease if they had the opportunity to receive a systemic therapy. In addition to Karnofsky prognostic score (KPS) and RPA, the graded-prognostic assessment (GPA) and diseases-specific GPA (DS-GPA) scores were calculated for further comparisons [9].

2.2. Treatment characteristics

Between January 2008 and June 2010, treatments were delivered on a Varian Clinac 2300 CD (Varian, Palo Alto, CA, USA) with a Brainlab M3 (Brainlab, Feldkirchen, Germany) micro multi leaf collimator (MLC). Head-positioning accuracy was ensured by the six degrees of freedom (6DoF) head plate with micrometrical screws (Brainlab AG, Feldkirchen, Germany) and verified with portal images. After June 2010, a dedicated Novalis TX (Varian, Palo Alto, CA, USA and Brainlab AG, Feldkirchen, Germany) was used with embarked high definition MLC and 6DoF robotic couch slaved to the ExacTrac X-Ray positioning system. A post-gadolinium enhanced T1-weighted magnetic resonance imaging (MRI) planning was obtained with a median time of eight days [range 1–34] after surgery. Head fixation was performed with patients in a supine position with double shell stereotactic thermoplastic masks from Brainlab AG (Feldkirchen, Germany). Stereotactic planning computed tomography (CT), planning MRI and postoperative MRI (if

available) were imported to iPlan RT image software (versions 3.5 to 4.2, Brainlab AG, Feldkirchen, Germany) for image registration and volumes delineation. The clinical target volume (CTV) included the resection cavity and any contrast enhancing lesion expanded by a 1 to (mostly) 2 mm margin. The planning target volume (PTV) margin was 0 (any SRS and SRT with Novalis Tx) or 1 mm (SRT with M3 MLC). Surrounding organs at risk (OAR) were delineated as well. Marginal dose prescription at the 70% isodose line and schedule (SRS or SRT) depended on the maximal diameter of the PTV: ≤ 2.0 cm = 18 Gy SRS; 2.1–3.0 cm = 15–16 Gy SRS; > 3.0 cm = 23.1 Gy in 3 fractions of 7.7 Gy SRT. The treatment delivery techniques used were either dynamic conformal arctherapy (DCA) or volumetric modulated arc therapy (VMAT) with 4–6 coplanar and non-coplanar arcs of 6 MV photons. Dose calculations were computed with iPlan RT dose (versions 3.5 and 4.0, Brainlab AG, Feldkirchen, Germany) or Varian Eclipse (versions 11 and 13, Varian, Palo Alto, CA, USA) treatment planning systems, for DCA and VMAT treatments, respectively.

2.3. Follow-up and salvage treatment

MRI (or contrasted CT-scan if contra-indicated) was performed 3-monthly for the first 18 months, then 6-monthly until 48 months post-SRS/SRT. A continuous increase in the size of a lesion (defined as area of contrast enhancement) and contrast uptake in at least two sequential MRI series, combined with a higher cerebral blood volume on perfusion sequences and/or symptoms without a satisfactory response to corticosteroids, was defined as LR. The differential diagnosis between tumor progression and radionecrosis (RN) was made with all clinical and radiological data available, including T2–, FLAIR–, unenhanced – and gadolinium – enhanced – T1 – and diffusion-weighted images, ADC-maps or perfusion-weighted images. In selected cases with inconclusive routine imaging, MRI spectroscopy or 18-Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) was added.

In case of LR or DBR, salvage WBRT was generally recommended for ≥ 4 active lesions, KPS < 70. Salvage focal treatment (SRS/SRT or surgery) was recommended in all other cases. All initial and salvage treatment options were discussed during multidisciplinary neuro-oncology tumor boards.

2.4. Statistical analysis

The Kaplan-Meier method was used to estimate median follow-up, OS, progression-free survival (PFS) and WFS. These were defined as time from date of surgery to date of death (OS), death or local relapse or distant relapse or lepto-meningeal relapse, whichever comes first (PFS) and death or salvage whole brain radiotherapy, whichever comes first (WFS). The cumulative incidence functions of LR and DBR were assessed within the competing risks framework with death as competing event.

The evaluation of the performance of a predictive tool (such as a nomogram) relies on calibration and discrimination [10]. The calibration measures the bias between mean predicted and observed proportions and is assessed with a plot of predicted against observed proportions. To evaluate the calibration of the nomogram, two subgroups of patients were constructed with respect to the patient score in the nomogram (superior or equal and inferior to the median). In each group, the observed WFS was plotted against the predicted WFS.

The discrimination measures the ability of the model to separate two groups based on the model predictions.

The discriminative ability was assessed at different time points with the area under the curve (AUC) of the receiver operating characteristic (ROC) or independently of a time point with the Harrell's concordance index [11]. All calculations were performed with R version 3.3.2 (R Foundation for Statistical Computing, Vienna, 2016).

Table 1
Demographics and clinical characteristics.

Characteristic	*n*	%
Patients	68	100
Male/female	39/29	–
Age (years)	Median 59.85 (44–84)	
<65	43	63.2
≥65	25	36.8
Primary disease		
NSCLC	42	61.8
Breast cancer	10	14.7
Renal cell carcinoma	3	4.4
Melanoma	3	4.4
Other	10	14.7
KPS		
<70	6	8.8
>=70	62	91.2
DS-GPA score		
0–2	11	16.2
2.5–3	41	60.3
>=3.5	9	13.2
NS	7	10.3
Extracranial metastases		
No	49	72
Stable	15	22
Progressive	4	6
Number of BM		
1	50	73.5
1–3	18	26.5

3. Results

Complete information for potential covariates were retrospectively recorded. Demographics and selected clinical characteristics are listed in Table 1. The median age was 60 years (range = 40–84). Most patients presented with neurological symptoms (88.2%), while in 11.8% BM was found incidentally. The most common primary tumor was non-small cell lung cancer (NSCLC) (61.8%). Breast cancer patients comprised 14.7% of whom 20% were HER-2 (+). Twenty-eight percent had extracranial metastases. The BM was unique in 70%.

The median follow-up of surviving patients was 63 months (range = 1–119 months). The median survival was 21 months (95% CI = 15–29). The 6-months and 12-months OS and PFS rates were 92% (95% CI = 86–99%), 71% (95% CI = 61–83%), 68% (95% CI = 58–80%) and 41% (95% CI = 31–55%), respectively. The 12-months cumulative incidence of LR and DBR were 15% (95% CI = 9–27%) and 34% (95% CI = 24–47%), respectively.

The chronological events and related treatments are summarized in the Table 2. The median time to the first brain failure was 10 months. First salvage SRS/SRT was performed in 14/40 patients (35%). Among the 12 patients who had a LR as the first event, 7 were treated with repeated SRS/SRT and 5 underwent salvage WBRT because of synchronous DBR. For those who developed isolated DBR, 19 were treated with salvage WBRT and seven with SRT/SRS. Second recurrences were noted in 10 patients (8 DBR, 2 LR + DBR simultaneously) after a median delay of 8.5 months. Five of them were treated with salvage WBRT. Only one patient developed a third LR treated with salvage WBRT. Overall, 44.1% were treated with salvage WBRT.

3.1. External validation of the WFS nomogram

The WFS rates at 6 and 12 months were 88% [95% CI = 81–97%] and 67% [95% CI = 56–81%], respectively (Fig. 1).

Table 2
Summary of salvage treatment according to chronology and site of recurrences.

First event			
Site (*n*)	Isolated LR (7)	DBR (28)	LR + DBR simultaneously (5)
Salvage TT (*n*)	SRT (4)	WBRT (19)	WBRT (5)
	SRT + surgery (3)	SRT (7)	
		Surgery (1)	
		BSC (1)	
Second event			
site	Isolated LR (0)	DBR (8)	LR + DBR simultaneously (2)
Salvage TT (*n*)	–	WBRT (4)	WBRT (1)
		SRT (3)	
		BSC (1)	
Third event			
Site (*n*)	LR (0)	DBR (0)	LR + DBR simultaneously (1)
Salvage TT (*n*)	–	–	WBRT (1)

BSC: best supportive care; DBR: distant brain relapse; LR: local relapse; SRT: stereotactic radiotherapy; TT: treatment; WBRT: whole brain radiotherapy.

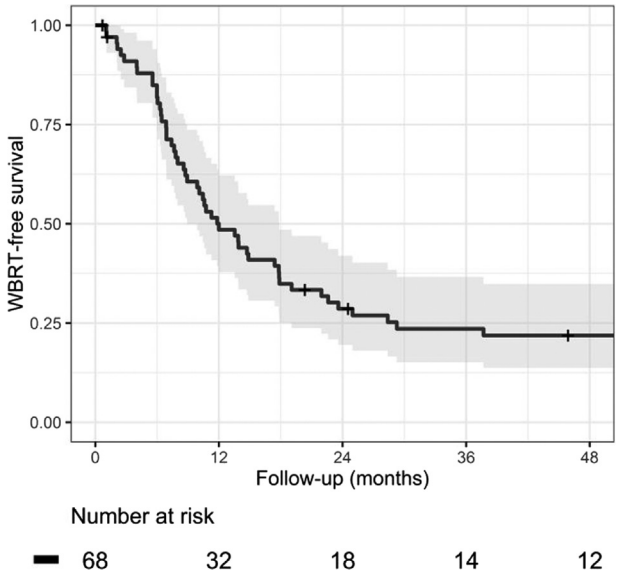

Fig. 1. Kaplan-Meier estimate of the WBRT-free survival in function of the time. The grey area around the curve represents the 95% confidence interval.

In order to assess the predictive performance of the WFS nomogram, we first tested the absence of bias of the predictive tool. The patient sample was divided in two groups according to their nomogram scores (superior or inferior to the median score) and the Kaplan-Meier estimates of the WFS at six and 12 months were plotted against the predicted WFS (Fig. 2). The calibration of the nomogram seemed poor with the 6 months WFS but correct with the 12 months WFS.

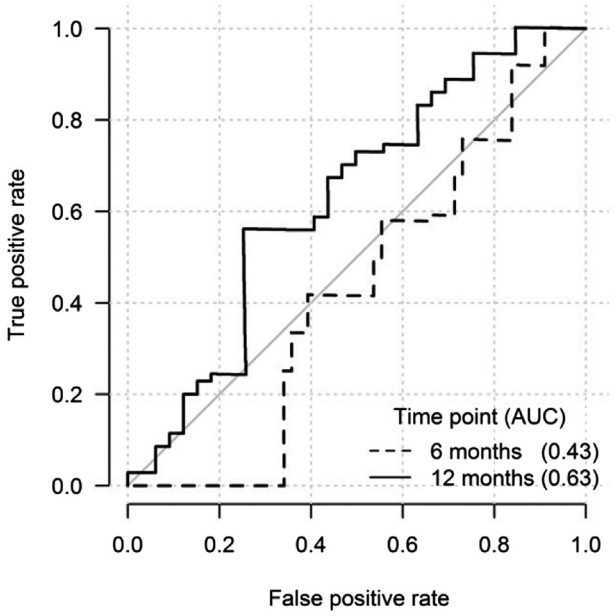

Fig. 3. Time-dependent receiver operating characteristic (ROC) curve describing the ability of the nomogram to discriminate, at two different time points (6 months = stripped line; 12 months = continuous line), patients for whom the event of interest (WBRT or death) is observed from the others.

We next assessed how the nomogram discriminates between patients that will, at a certain time point, present the event (death or WBRT) and patients who will not. This was done through calculating the AUC of the ROC curve (Fig. 3). At 6 and 12 months, the AUC of the nomogram's predictions were 0.43 and 0.63, respectively.

Finally, we checked whether predictive scores were correlated with the time before an event (death or WBRT) is observed. The Harrel's c index [95% confidence interval] was 0.54 [0.45–0.62].

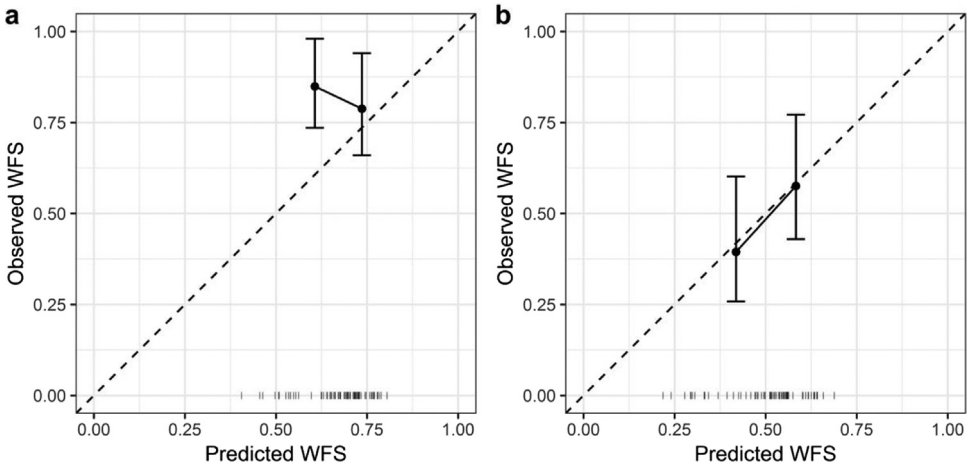

Fig. 2. Calibration plots for WFS at 6 (a) and 12 months (b): the average observed, Kaplan-Meier estimate of the WFS was plotted against the nomogram-predicted WFS. The dashed line indicates a perfect calibration of the model. Each point represents the average predicted and observed WFS of half of the sample. Error bars represent the limits of the 95% confidence interval on the observed value. WFS is underestimated at 6 months but correctly estimated at 12 months.

4. Discussion

In the postoperative setting of BM, WBRT has long been a standard to reduce the risk of LR. SRS is an alternative to avoid or delay WBRT. In a randomized trial, SRS was demonstrated to be superior in terms of cognition, without significant impact on OS but at the cost of higher LR and DBR rates [5]. In the current era of personalized medicine, the choice of WBRT or SRS is thus a question of selection of the right technique for the right patient. A predictive nomogram was developed based on a multi-institutional dataset of 895 patients with 2095 BM treated with SRS without prior WBRT, among which 11.7% were previously resected [8]. The independently weighted hazard ratio was used to create a nomogram to display estimated probabilities of 6 and 12-months WFS with a corrected Harrell's C concordance index of 0.62. We sought to retrospectively validate this WFS predictive nomogram in a mono-institutional study of 68 patients having received postoperative SRS/SRT for BM. In terms of calibration, the 6 months rate was underestimated by the nomogram, while it was accurately predicted at 12 months. The discriminative power of the nomogram's prediction was, however, quite poor with AUC of the ROC of 0.43 and 0.63 at 6 and 12 months, respectively and a Harrell's c concordance index of 0.54, close to the minimum of 0.5. The nomogram is thus relatively well calibrated but poorly discriminative.

Anyway, different limitations are inherent to our study. It is a retrospective study on a relatively small group of 68 patients treated with treatment algorithms that pertain to our center and the referring neurosurgical network. This is illustrated by the median time to salvage WBRT of 10.7 months in our series in comparison to 6.2 months in the original nomogram publication. The fact that 35% of our patients were treated with SRS/SRT as first salvage treatment may have played a role. It may also reflect a more rigorous selection of patients being operated, most often for a single BM and thus an intrinsic superior prognosis [12], with a median survival of 23 months compared to 9.8 months in the nomogram publication. Beyond the patient selection bias, it is a highly heterogeneous population of metastatic patients with variable prognosis factors inherent to the primary tumors and their intrinsic aggressivity and therapeutic sensitivity characteristics. Last, most patients were treated in a period of time when molecular biology knowledge was stammering. Nowadays, the routine recognition of these characteristics and the increasing number of targeted therapies that profoundly modulate the general and brain-specific prognosis of the patients may simply invalidate the applicability of such nomograms that do not or only poorly integrate them.

Contrary to a prognostic index like the DS-GPA that aim to categorize groups of patients with a relatively similar prognosis, nomograms are statistics tools aimed at individually estimating the prognosis of a given disease condition. A recent review identified and extensively analyzed the different published nomograms derived from cohorts of patients with BM from solid tumors, stratified by endpoints [13]. They identified 6 nomograms predicting the OS, 1 the risk of new BM [14], and 1 the WFS [8]. Only 4 studies included external validation cohorts and concordance indexes varied from 0.60 to 0.79. The authors pointed out the systematic bias of the prognosticators selection limits, linked to the retrospective nature of the databases and the absence of some well-known prognosticators. They also underlined the fast-moving knowledge of biomolecular characteristics and their impact on OS and disease control, that is already reflected in molecular-based adaptations of the DS-GPA prognostic index for lung cancer [15] and malignant melanoma [5]. Anyway, they noticed that nomograms predicting OS systematically outperformed prognostic indexes like RPA or DS-GPA.

The recent introduction of ICI in the therapeutic armament also profoundly modified both the general and the brain-specific prognosis of patients with metastases from lung, melanoma and kidney cancer. In a large retrospective monocentric study on 260 patients with a total of 623 BM, it was shown that the concurrent use of ICI with SRS/SRT significantly improved the OS to 24.7 months compared to 12.9–14.5 months in case of SRS/SRT without or with non-concomitant ICI. Moreover, the mean number of new BM following SRS/SRT was 4 in case of SRS/SRT alone or non-concomitant ICI, and 2 in case of concomitant ICI [16,17].

The large and increasing number of parameters predicting the outcome and their relative weight to each other indicate a need for improved prediction methods [18]. Utilizing bioinformatics to perform data mining will undoubtedly help to solve the problem. The mutual information and rough set of particle swarm optimization (MIRSPSO) is a machine learning algorithm, trained on 446 BM patients treated with SRS, that outperformed other statistical methods to predict the OS of 254 test patients with an AUC of 0.98 [19].

5. Conclusion

In an independent retrospective dataset of 68 patients having been treated with postoperative SRS/SRT for a BM, this nomogram underestimated the 6-months WFS and correctly estimated it at 12 months. Anyway, the discriminative power was poor with a concordance index of 0.54. These results reflect the heterogeneity of the BM patients, the bias in selection criteria applied by each center and the delay in integrating the novel biomolecular diagnostic tools and treatments in such nomograms. The larger amount of data to handle will be best managed by artificial intelligence algorithms.

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Disclosure of interest

The authors declare that they have no competing interest.

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