Individualized early death and long-term survival prediction after stereotactic radiosurgery for brain metastases of non-small cell lung cancer

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Brain metastases

Individualized early death and long-term survival prediction after stereotactic radiosurgery for brain metastases of non-small cell lung cancer: Two externally validated nomograms

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ABSTRACT

Introduction: Commonly used clinical models for survival prediction after stereotactic radiosurgery (SRS) for brain metastases (BMs) are limited by the lack of individual risk scores and disproportionate prognostic groups. In this study, two nomograms were developed to overcome these limitations.

Methods: 495 patients with BMs of NSCLC treated with SRS for a limited number of BMs in four Dutch radiation oncology centers were identified and divided in a training cohort ($n = 214$, patients treated in one hospital) and an external validation cohort $n = 281$, patients treated in three other hospitals). Using the training cohort, nomograms were developed for prediction of early death (<3 months) and long-term survival (>12 months) with prognostic factors for survival. Accuracy of prediction was defined as the area under the curve (AUC) by receiver operating characteristics analysis for prediction of early death and long term survival. The accuracy of the nomograms was also tested in the external validation cohort.

Results: Prognostic factors for survival were: WHO performance status, presence of extracranial metastases, age, GTV largest BM, and gender. Number of brain metastases and primary tumor control were not prognostic factors for survival. In the external validation cohort, the nomogram predicted early death statistically significantly better ($p < 0.05$) than the unfavorable groups of the RPA, DS-GPA, GGS, SIR, and Rades 2015 (AUC = 0.70 *versus* range AUCs = 0.51–0.60 respectively). With an AUC of 0.67, the other nomogram predicted 1 year survival statistically significantly better ($p < 0.05$) than the favorable groups of four models (range AUCs = 0.57–0.61), except for the SIR (AUC = 0.64, $p = 0.34$). The models are available on www.predictcancer.org.

Conclusion: The nomograms predicted early death and long-term survival more accurately than commonly used prognostic scores after SRS for a limited number of BMs of NSCLC. Moreover these nomograms enable individualized probability assessment and are easy into use in routine clinical practice.

Stereotactic Radiosurgery (SRS) is an established treatment for a limited number of brain metastases (BMs) with a maximum diameter up to 4 cm [1]. To predict survival in BM patients, several prognostic models have been published in the past decades [2–4]. The most commonly used is the Recursive Partitioning Analysis (RPA), which is a relatively simple scoring system, initially developed in patients who were treated with whole brain radiotherapy (WBRT), and subsequently validated for other treatment modalities [5]. RPA classification takes into account age, presence of extracranial metastases, primary tumor control, and performance status. The RPA divides the patient cohort into three prognostic categories; however, a major disadvantage of the RPA is that approximately two-third of patients suitable for SRS will fall in the intermediate prognostic class, and probabilities for both short and long-term survival are group-based and not individualized [2]. Lack of individualized survival probability and

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disproportional size of prognostic groups were also observed in other more recently published prognostic models for survival, such as the Golden Grading System (GGS), Disease-Specific Graded Prognostic Assessment (DS-GPA), Score Index for Radiosurgery in brain metastases (SIR), and Rades 2015 [2,6–12]. With nomograms, however, it is possible to assess individualized probabilities for endpoints, and relevant prognostic factors can be evaluated. In this study, two validated nomograms were developed for the prediction of early death (<3 months) and long-term (>1 year) survival of patients treated with SRS for a maximum of four BMs of NSCLC. The rationales for these endpoints were that (1) accurate prediction of early death can be relevant for SRS patient selection, and (2) accurate prediction of long-term survival can be particularly useful for the choice of either radical or palliative treatment of extracranial disease [13,14].

Materials and methods

Data

This multicenter cohort study was approved by the local institutional review board of MAASTRO clinic and registered at ClinicalTrials.gov (NCT02265549). Clinical data were collected from all patients with newly diagnosed BMs treated with linear accelerator-based SRS between December 2002 and March 2015 in four participating Dutch Radiation Oncology centers: MAASTRO clinic in Maastricht (MC), VU University medical center (VUmc) in Amsterdam, Verbeeten Institute in Tilburg (VT), and Catharina Hospital in Eindhoven (CZE). Patients were generally eligible for SRS if they had a maximum of three BMs, with a maximum diameter of 4 cm, on diagnostic magnetic resonance imaging (MRI) performed by the referring hospital. Prior to treatment, a contrast enhanced high-resolution MRI serving radiation planning purposes was performed with three-dimensional distortion correction. If a fourth BM was identified on this planning-MRI, three of the four participating centers also treated these patients with SRS as the single treatment modality. The gross tumor volume (GTV) was defined as the contrast enhancement on the planning-MRI. An isotropic margin of 1–3 mm was used to generate the planning target volume (PTV) [15]. SRS dose was prescribed at the PTV in the range of 15–24 Gy in one to three fractions. Treatment planning in VUmc and CZE have been described previously [2,15]. MC used iPlan (Brainlab AG, Feldkirchen, Germany) and Eclipse (Varian, Palo Alto) software, and treatment planning was performed with non-coplanar dynamic conformal arcs or coplanar volumetric modulated arc therapy (VMAT). At VT, the XiO software (Elekta, Stockholm, Sweden) was used for treatment planning, which was accomplished with a non-coplanar static arcs technique or VMAT. During follow-up, MRI scans were acquired every three months; an outpatient visit was planned if both the physical and mental conditions of the patient allowed it.

Variable selection

A database was available of all patients treated with SRS for newly diagnosed brain metastases of several primary tumors ($n = 929$) in four Dutch hospitals. For this study, patients with BM of NSCLC from whom the date of death was known, or patients with BM of NSCLC who had a follow-up of at least of 1 year were selected ($n = 495$). In the training cohort ($n = 214$) Kaplan–Meier analysis including multivariate Cox regression analysis was performed on the baseline characteristics to identify significant prognostic factors for survival. Dependent prognostic factors were excluded from the multivariate analysis: PTV largest BM is dependent on GTV largest BM; cumulative GTV is dependent on GTV largest metastasis; and dose is dependent on GTV largest BM. In the training cohort, the following baseline characteristics were statistically significant prognostic factors for survival in multivariate cox regression analysis: WHO performance status ($p < 0.01$, beta regression coefficient (β) = 0.41, odds ratio (OR) = 1.50, 95% confidence interval (95% CI) = 1.20–1.88), presence of extracranial metastases ($p < 0.01$, $\beta = 0.73$, OR = 2.08, 95% CI = 1.44–3.00), age ($p < 0.01$, $\beta = 0.03$, OR = 1.03, 95% CI = 1.02–1.05), GTV largest BM ($p = 0.01$, $\beta = 0.03$, OR = 1.03, 95% CI = 1.01–1.06), and gender ($p = 0.04$, $\beta = -0.35$, OR = 0.70, 95% CI 0.51–0.98); Other baseline characteristics were not prognostic for survival: primary tumor control ($p = 0.98$), and number of treated BM ($p = 0.18$).

Nomograms

The patient cohort treated in the VUmc ($n = 214$) was used as the training cohort for development of the two nomograms. The other patient cohort ($n = 281$, patients treated in MC, VT, and CZE) was used as an external validation cohort in which the two developed nomograms were tested independently from the training cohort. Prognostic factors for survival identified with Cox multivariate analysis in the training cohort of patients ($n = 214$) were used to develop the nomograms for the prediction of early death (<3 months) and long-term survival (>1 year), respectively. Nomograms were made based on logistic regression analysis and learned on the VUmc cohort. The primary endpoint of this study was the area under the curve (AUC) obtained using receiver operating characteristics (ROC) analysis for early death and long-term survival prediction. In the training and validation cohorts, the AUCs of the developed nomogram models were compared with the AUCs of the RPA, DS-GPA, GGS, SIR, and Rades 2015 prognostic models. Comparison of ROC curves was done using DeLong's test for correlated ROC curves. Statistical analyses were performed using SPSS (version 23, IBM, New York), using R (version 3.1.3, R Foundation for Statistical Computing, Vienna, Austria) using the rms, PredictABEL, and pROC packages. Validation was performed according to established methods [16]. Calculating AUC confidence intervals and calibration R2 values (predicted *versus* observed risk) was done according previously described methods [17,18].

Results

Median survival of the total cohort of patients ($n = 495$) was 6.8 months. Baseline characteristics of the training ($n = 214$) and validation ($n = 281$) cohorts are shown in Table 1.

The first developed nomogram specific for the prediction of early death is shown in Fig. 1 containing the previously identified prognostic factors for survival. With an AUC of 0.77, the nomogram predicted early death statistically significantly better than the unfavorable groups of the RPA, DS-GPA, GGS, SIR, and Rades 2015 (range AUC = 0.52–0.59). Similar results were observed in the external validation cohort with an AUC = 0.70 of the nomogram *versus* range AUCs = 0.51–0.60 with the other prognostic models, Table 2). For the ROC curves of the nomogram, see Supplementary materials 1. Calibration curves (predicted *versus* observed probability) of the nomogram are shown in Supplementary materials 2 with R2 values of 0.98 and 0.82 in respectively the training and validation cohort.

The independently developed second nomogram is specific for the prediction of long-term survival and shown in Fig. 2 containing the same prognostic factors for survival, but otherwise ranked in the nomogram. With an AUC = 0.77, this nomogram predicted 1 year survival statistically significantly better than the favorable groups of the RPA, DS-GPA, GGS, SIR, and Rades 2015 in the training cohort (range AUCs = 0.55–0.68, Table 2). In the external validation cohort comparable results were observed with AUC = 0.67 of the nomogram *versus* range AUCs = 0.57–0.61, $p < 0.05$ of four

Table 1
Characteristics of training and validation cohort of 495 patients treated with SRS for BM of NSCLC.

	Training cohort $n = 214$	External validation cohort $n = 281$
Radiation Oncology center		
VUmc	100%	0%
MC	0%	55%
VT	0%	25%
CE	0%	20%
Gender		
Female	47%	46%
Male	53%	54%
Mean age ± SD (years)	63 ± 10	63 ± 11
WHO performance score		
0 or 1	75%	83%
2	12%	16%
3	4%	1%
Unknown	9%	0%
Number of BM lesions		
1	66%	64%
2	30%	24%
3	4%	11%
4	0%	1%
Extracranial metastases		
Yes	38%	26%
No	62%	74%
Primary tumor control		
Yes	41%	55%
No	59%	45%
Mean GTV of largest BM (cm^3) ± SD	6.8 ± 6.6	7.3 ± 7.9
RPA		
Favorable	30%	33%
Intermediate	54%	60%
Unfavorable	16%	17%
DS-GPA		
Favorable	7%	11%
Intermediate	87%	82%
Unfavorable	6%	7%
GGS		
Favorable	29%	33%
Intermediate	67%	63%
Unfavorable	4%	4%
SIR		
Favorable	29%	33%
Intermediate	69%	65%
Unfavorable	2%	2%
Rades 2015		
Unfavorable	24%	25%
Favorable	76%	75%
Median survival (95% CI)	6.3 (5.0–7.6)	7.0 (6.0–8.1)
Death at 3 months	33%	24%
Alive at 1 year	36%	30%

of the five other prognostic models (Table 2). Although the AUC of the nomogram was higher than that of the favorable prognostic group of the SIR (0.67 *versus* 0.64, $p = 0.34$), this difference was not statistically significant. ROC curves of the nomogram are provided in Supplementary materials 3. Calibration curves (predicted *versus* observed probability) of the nomogram are shown in Supplementary materials 4 with R2 values of 0.97 and 0.76 in respectively the training and validation cohort. The training cohort was divided in three equal sized groups based on the probability of 1 year survival as determined by the nomogram. The probability on 1 year survival per patient ranged in the first, second, and third group respectively from <24%, 24–47%, and >47%. There was a statistically significant difference in survival between the three risk groups in both the training as the validation cohort with Kaplan–Meyer analysis and log-rank test ($p < 0.001$, Supplementary materials 5). Long term survival over several years was mainly seen in the favorable (>47% one year survival probability) groups of both the training as the validation cohort. Regression coefficients and other characteristics of both the nomogram for early death prediction as the nomogram for long term survival prediction are provided in Supplementary materials 6.

Discussion

Current published models for the prediction of survival of BM patients treated with SRS have several limitations for clinical applicability, and are mainly limited by the lack of individualized probability assessment. Most published models were developed in or included patients who were treated with other modalities such as WBRT, surgery, or a combination of SRS and WBRT. These models have an unbalanced patient distribution in common, with only a small proportion of patients in the favorable- and unfavorable prognostic category, which are the most relevant for clinical decision making. However, the major limitation is that none of the prognostic models have an individualized probability assessment of survival; rather, they distribute patients only according to a prognostic groups, which is undesirable in the current era of personalized medicine [2].

In this study, nomograms were developed for the prediction of early death (<3 months) and long-term survival (>1 year), respectively, in patients treated with SRS for BM of NSCLC. The models were based on and validated in a homogeneous cohort of patients, with a maximum of four BM lesions each, who were treated with SRS alone in four Dutch radiation oncology centers. The nomogram allows for an upfront calculation of the probability of early death and long-term survival on an individual patient basis. Prediction of early death is of relevance for patient selection for SRS to avoid overtreatment of patients. Prediction of long-term survival is of particular relevance when determining extracranial treatment strategies. In patients with a relatively high chance of surviving more than one year, more aggressive therapy for extracranial disease sites may be beneficial to maintain long-term quality of life and disease control [19,20].

Our first nomogram predicts early death more accurately than the unfavorable groups of the RPA, GGS, DS-GPA, SIR, and Rades 2015 in both the training as the validation cohorts. Our second nomogram predicted long term survival more accurately than the favorable groups of the RPA, DS-GPA, GGS, SIR, and Rades 2015 in the training cohort. It has to be noted that in the validation cohort the nomogram predicted long term survival better than the other prognostic models except the SIR. However, the nomogram has still the advantage over the SIR that there is an individualized probability assessment instead of a group based probability assessment. Moreover, the nomogram is easier in use than the SIR in routine clinical practice. It is important to further validate these nomograms in other BM populations treated with SRS, within and outside the Netherlands. Moreover, it is of interest to assess the applicability of these nomogram models for patients with more than four BM lesions, especially as the number of lesions was found not to be an important prognostic factor in patients treated with SRS alone in this study [21].

The choice to only include NSCLC patients in this model was based on the fact that the proportion of other primary tumors was relatively small in our database of in total 929 patients treated with SRS for BM in four Dutch hospitals. Therefore, we questioned the applicability of our nomograms for other primary tumors than NSCLC. Combining datasets of patients treated with SRS for BM of other primary tumors than NSCLC may allow the development of predictive models per tumor type. The data to develop models

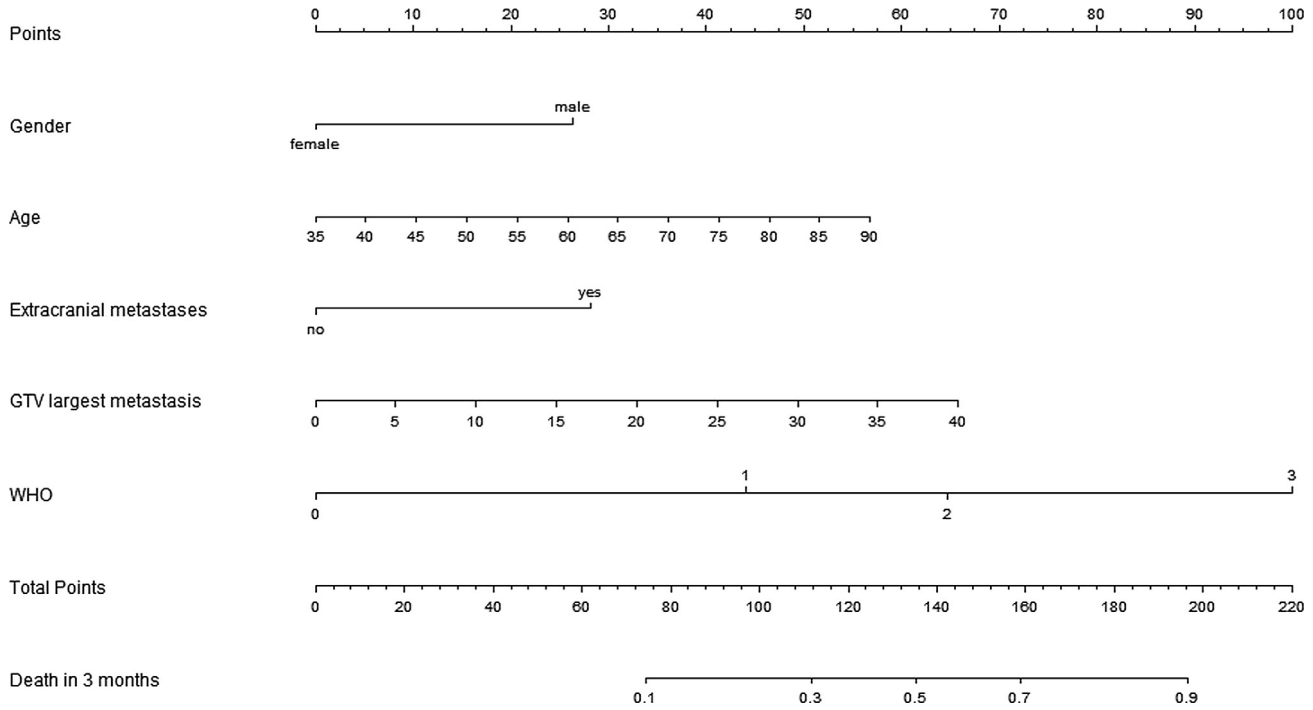

Fig. 1. Nomogram for prediction of early death based on outcome of 214 patients treated with SRS alone for BM of NSCLC. Legend: SRS = stereotactic radiosurgery, BM = brain metastasis, NSCLC = non-small cell lung cancer, WHO = World Health Organization performance status, GTV = gross tumor volume, extramets = extracranial metastases.

Table 2
Accuracy of prediction of respectively early death (<3 months) and long term survival (>1 year) of two nomograms compared to the unfavorable and favorable prognostic groups of the RPA, DS-GPA, GGS, SIR, and Rades 2015 using ROC analysis.

Early death prediction (<3 months)	AUC in training cohort for early death prediction $n = 214$	p-Value compared to nomogram	AUC in validation cohort for early death prediction $n = 281$	p-Value compared to nomogram
Nomogram early death	0.79 (95% CI: 0.72–0.86)	–	0.70 (95 CI: 0.63–0.77)	–
RPA Unfavorable	0.59 (95% CI 0.52–0.65)	$p < 0.01$	0.55 (95% CI 0.49–0.61)	$p < 0.01$
DS-GPA Unfavorable	0.54 (95% CI 0.50–0.59)	$p < 0.01$	0.56 (95% CI 0.51–0.61)	$p < 0.01$
GGS Unfavorable	0.53 (95% CI 0.50–0.57)	$p < 0.01$	0.54 (95% CI 0.50–0.57)	$p < 0.01$
SIR Unfavorable	0.52 (95% CI 0.49–0.55)	$p < 0.01$	0.51 (95% CI 0.49–0.53)	$p < 0.01$
Rades 2015 Unfavorable	0.57 (95% CI 0.51–0.63)	$p < 0.01$	0.60 (95% CI 0.56–0.65)	$p < 0.01$
Long term survival prediction (>1 year)	AUC in training cohort for long term survival prediction $n = 214$	p-value compared to nomogram	AUC in validation cohort for long term survival prediction $n = 281$	p-value compared to nomogram
Nomogram long term survival	0.77 (95% CI: 0.70–0.84)	–	0.67 (95% CI: 0.60–0.73)	–
RPA favorable	0.66 (95% CI 0.60–0.73)	$p < 0.01$	0.61 (95% CI 0.55–0.67)	$p = 0.04$
DS-GPA Favorable	0.55 (95% CI 0.51–0.60)	$p < 0.01$	0.57 (95% CI 0.52–0.62)	$p < 0.01$
GGS Favorable	0.66 (95% CI 0.60–0.73)	$p < 0.01$	0.61 (95% CI 0.55–0.67)	$p = 0.04$
SIR Favorable	0.68 (95% CI 0.61–0.74)	$p < 0.01$	0.64 (95% CI 0.58–0.71)	$p = 0.34$
Rades 2015 Favorable	0.61 (95% CI 0.55–0.68)	$p < 0.01$	0.60 (95% CI 0.54–0.66)	$p = 0.02$

for these outcomes is readily available from centers worldwide. Unfortunately, sharing these data is hampered by political, legal, ethical and administrative boundaries. In order to circumvent these boundaries, a distributed learning approach can be employed [22]. In the distributed learning approach, a model application is sent to each hospital. There, the model learns from the data and is sent back to the modeler. Each locally learned model is combined into a global model that integrates the knowledge of all locally learned models. Using this approach, privacy sensitive patient data never leaves the center. In the future, we intend to use a distributed learning strategy to develop more nomogram models for BM patients.

Despite the use of multiple relevant prognostic factors there is still opportunity for improvement for the accuracy of the nomograms. Further research should focus on improving the accuracy of survival prediction by incorporating additional factors, e.g., using radiographic analysis of the primary tumor or BM (Radiomics), and assessing the value of biomarkers [23–27]. These tools may contribute to more accurate survival prediction, although clinical applicability may be complex and challenging. Therefore, risk assessment based on clinical factors alone remains valuable and relevant for many hospitals that do not have the capacity to perform radiomics and/or biomarker analysis. Accurate prediction of survival, local control, distant brain recurrence, and toxicity is important for patients and clinicians regarding the choice for treatment options; this is also known as *shared decision* [28–33]. Shared decision will be possible if the patient is informed by individualized probabilities for clear endpoints, such as early death within 3 months and long term survival over 1 year. With these probabilities available and guidance of the physician for

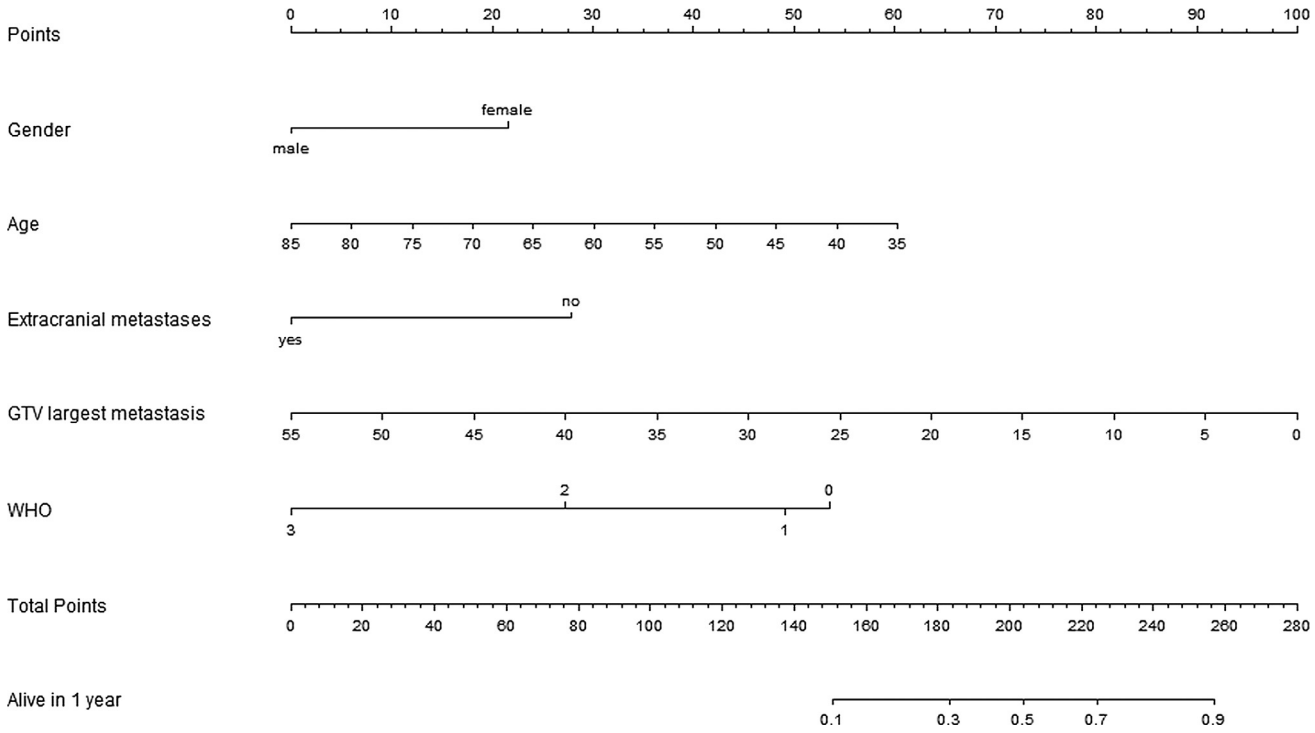

Fig. 2. Nomogram for prediction of long-term survival based on outcome of 214 patients treated with SRS alone for BM of NSCLC. Legend: SRS = stereotactic radiosurgery, BM = brain metastasis, NSCLC = non-small cell lung cancer, WHO = World Health Organization performance status, GTV = gross tumor volume, extramets = extracranial metastases.

interpretation, the patient together with his family may be able to choose between treatment options. The limitations of our study are the retrospective design and the risk of selection bias, although the developed nomograms are based on outcome data in routine clinical practice. These nomograms cannot be used for patients with very large BM of more than 4 cm in diameter, patients with more than 3 brain metastases, or patients treated with other modalities than SRS alone for newly diagnosed BM of NSCLC. The strength of our study is the external validation of both nomograms.

In conclusion, two novel clinical nomogram models were developed and validated for the prediction of respectively early death (<3 months) and long-term (>1 year) survival after SRS for patients with a maximum of four BMs of NSCLC. These nomogram models can be used for individual probability assessments, and to avoid the limitations of previously published prognostic classification systems. The nomograms can be found at www.predictcancer.org.

Conflicts of interest with respect to this research paper

None.

Conflicts of interests not related to this work

(1) Department of radiotherapy MAASTRO Clinic has a research agreement with Varian Medical Systems, Palo Alto USA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.02.006.

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