ANTICANCER RESEARCH *40*: 3499-3504 (2020)
doi:10.21873/anticanres.14337

Occurrence of Seizures Prior to Single-fraction Radiosurgery or Multi-fraction Stereotactic Radiotherapy in Patients With Very Few Brain Metastases

DIRK RADES[1], JASPAR WITTELER[1], TROELS W. KJAER[2], SOEREN TVILSTED[3] and STEVEN E. SCHILD[4]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Neurological Department, Zealand University Hospital, Roskilde, Denmark;*
[3]*Research Projects and Clinical Optimization, Zealand University Hospital, Koege, Denmark;*
[4]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Background/Aim: Seizures represent a major problem for patients with brain metastases. This study evaluated the role of seizures in patients receiving single-fraction radiosurgery (SRS) or multi-fraction stereotactic radiotherapy (FSRT). Patients and Methods: This retrospective study included 195 patients receiving SRS (n=164) or FSRT (n=31) alone for one to three brain metastases. The prevalence of pre-SRS/FSRT seizures and correlations with pre-treatment factors were investigated. These factors plus pre-SRS/FSRT seizures were assessed in regard to survival. Results: Thirty-three patients had pre-SRS/FSRT seizures (prevalence=16.9%). Seizures were significantly correlated with age ≤61 years. Trends were observed for seizures being more frequent in those with NSCLC and those without extra-cranial metastatic spread. On multivariate analysis, significant associations with improved survival were found for Karnofsky performance score ≥80%, breast cancer, and an interval from diagnosis of malignant disease to SRS/FSRT ≥21 months. Conclusion: Younger age, NSCLC and absence of extra-cranial spread appeared to be risk factors for seizures prior to SRS/FSRT. Having seizures prior to SRS/FSRT showed no association with survival.*

Cerebral metastases represent a serious palliative situation for patients with malignant diseases (1-6). The majority of these patients have already multiple (more than three) intracerebral lesions at the time of diagnosis of metastatic spread to the brain (1, 2, 6). Many of these patients have very poor prognoses and receive whole-brain radiotherapy alone. The expected survival of patients with limited brain metastasis, *i.e.* one to three lesions, is generally more favorable, and these patients are often candidates for local therapies, either alone or combined with whole-brain radiotherapy (1, 6). Local therapies include stereotactic radiosurgery (SRS), which is given with a single fraction; fractionated stereotactic radiotherapy (FSRT), which mostly consists of three to seven fractions; and resection of metastases (1, 6-8). Most of these patients are treated with SRS or FSRT. Depending on the risk of intracerebral recurrence, SRS and FSRT are administered with or without whole-brain radiotherapy. According to randomized trials, the addition of whole-brain radiotherapy increased the risk of post-treatment cognitive decline but improved long-term intracerebral control of the disease (9, 10). Intracerebral progression or recurrence can also be associated with cognitive impairment (11-13). Therefore, patients with a higher risk of developing new or progressive brain metastases likely benefit from the addition of whole-brain radiotherapy, whereas those patients with a lower risk appear to be better treated with SRS or FSRT alone (14). The present study focused on patients of the latter group. The quality of life of these patients can be significantly compromised by seizures that most often occur prior to treatment of brain metastases (15). The risk of seizures was reported to be associated with the number of intracerebral lesions (16, 17). Therefore, it is reasonable to investigate the role of seizures separately for patients with single, few and multiple lesions. This study was performed on patients treated with SRS or FSRT alone for a limited number of one to three metastases. It evaluated the prevalence of seizures prior to SRS/FSRT, risk factors for this condition, and potential associations of seizures with survival in a large cohort of patients.

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 451 50045401, Fax: +49 451 50045404, e-mail: dirk.rades@uksh.de

Key Words: Brain metastases, radiosurgery, stereotactic radiotherapy, seizures.

Patients and Methods

This retrospective study included 195 patients treated with single-fraction SRS (n=164) or multi-fraction FSRT (n=31) for one to three brain metastases between 1999 and 2019. It was approved by the local Ethics Committee of the University of Lübeck (reference-number: 20-120A). The median dose of single-fraction SRS was 20 Gy (range=15-25 Gy). FSRT was administered with total doses ranging between 22.5 and 45 Gy (median=33 Gy); the median number of fractions was 3 (range: 5-16), and the median dose per fraction was 8 Gy (range=2.5-12 Gy). In the entire cohort, the prevalence of seizures prior to SRS or FSRT was determined. In addition, correlations between seizures and seven potential prognostic pre-treatment factors (Table I) were investigated. These factors included age at SRS or FSRT (≤61 *versus* ≥62 years, median=62 years), gender, Karnofsky performance score (≤70% *versus* ≥80%, median=80%), type of primary tumor [breast cancer *versus* non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma and other types (n<20)], number of brain metastases (one *versus* two or three), extra-cranial metastatic spread (absence *versus* presence) and interval from first diagnosis of malignant disease to SRS or FSRT (≤20 *versus* ≥21 months, median=20 months). Furthermore, these factors plus symptoms and seizures prior to SRS or FSRT (Table I) were assessed for associations with survival.

For the analyses of correlations between seizures prior to SRS or FSRT and the potential prognostic pre-treatment factors, the chi-square test was applied. *p*-Values of less than 0.05 were considered to indicate a significant correlation, and *p*-values <0.12 were considered to show a trend. Survival times were calculated from the day of single-fraction SRS or the day of the first fraction of FSRT. For univariate analyses of survival, the Kaplan–Meier method and the log-rank test were applied. In the case of a significant correlation ($p<0.05$) or a trend ($p<0.12$), the factors were additionally analyzed in a multivariate Cox regression analysis. When a *p*-value was found to be less than 0.05 in the Cox regression analysis, the prognostic factor was considered to be independent.

Table I. *Distribution of the potential prognostic factors investigated in this study.*

Potential prognostic factor	Number of patients, (%)
Symptoms prior to SRS/FSRT	
No symptoms	41 (21.0)
Seizures alone	19 (9.7)
Other symptoms alone	121 (62.1)
Seizures + other symptoms	14 (7.2)
Seizures prior to SRS/FSRT	
No seizures	162 (83.1)
Seizures	33 (16.9)
Dose of SRS/FSRT (EQD2)	
<20 Gy	26 (13.3)
20 Gy	102 (52.3)
>20 Gy	67 (34.4)
Age at SRS/FSRT	
≤61 Years	97 (49.7)
≥62 Years	98 (50.3)
Gender	
Female	96 (49.2)
Male	99 (50.8)
Karnofsky performance score	
≤70%	64 (32.8)
≥80%	131 (67.2)
Type of primary tumor	
Breast cancer	27 (13.8)
NSCLC	71 (36.4)
RCC	22 (11.3)
Melanoma	45 (23.1)
Other types	30 (15.4)
Number of brain metastases	
One	117 (60.0)
Two or three	78 (40.0)
Extra-cranial metastatic spread	
Absence	82 (42.1)
Presence	113 (57.9)
Interval from first diagnosis of malignant disease to SRS/FSRT	
≤20 Months	98 (50.3)
≥21 Months	97 (49.7)

SRS: Single-fraction tereotactic radiosurgery; FSRT: fractionated stereotactic radiotherapy; EQD2: equivalent dose in 2 Gy fractions; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

Results

For 33 out of the 195 patients included in this study, seizures prior to SRS or FSRT were documented, corresponding to a prevalence of 16.9%. The occurrence of seizures was significantly correlated with age ≤61 years (prevalence of 24.7%, $p=0.008$). Trends were observed for seizures being more frequent in those with NSCLC (26.7%, $p=0.113$) and those without extra-cranial metastatic spread (23.2%, $p=0.072$). The results of this analysis are shown in Table II.

Moreover, a significant association with improved survival was found in those with a Karnofsky performance score of ≥80% ($p<0.001$) on univariate analysis (Table III), and trends were observed for improved survival in those with breast cancer ($p=0.059$), without extra-cranial metastatic spread ($p=0.068$), and an interval from first diagnosis of malignant disease to SRS or FSRT of ≥21 months ($p=0.055$). Symptoms ($p=0.181$) and seizures ($p=0.431$) prior to SRS or FSRT were not correlated with survival. In the corresponding multivariate Cox regression analysis, a Karnofsky performance score of ≥80% ($p<0.001$), a favorable type of primary tumor (*i.e.* breast cancer) ($p=0.038$) and an interval from first diagnosis of the malignant disease to SRS or FSRT of ≥21 months ($p=0.005$) proved to be independent predictors of survival (Table IV).

Discussion

Patients with very few brain metastases often receive SRS or FSRT, which are administered either alone or as a boost following whole-brain radiotherapy (1, 5, 6). Since two

Table II. *Correlations between potential prognostic pre-treatment factors and seizures prior to single-fraction (SRS) or fractionated (FSRT) stereotactic radiotherapy.*

Potential prognostic factor	Patients with seizures, N (%)	*p*-Value
Age at SRS/FSRT		
≤61 Years	24 (24.7)	**0.008**
≥62 Years	9 (9.2)	
Gender		
Female	16 (16.7)	0.944
Male	17 (17.2)	
Karnofsky performance score		
≤70%	13 (20.3)	0.414
≥80%	20 (15.3)	
Type of primary tumor		
Breast cancer	5 (18.5)	0.113
NSCLC	19 (26.7)	
RCC	2 (9.1)	
Melanoma	4 (8.9)	
Other types	3 (10.0)	
Number of brain metastases		
One	22 (18.8)	0.434
Two or three	11 (14.1)	
Extra-cranial metastatic spread		
Absence	19 (23.2)	0.072
Presence	14 (12.4)	
Interval from first diagnosis of malignant disease to SRS/FSRT		
≤20 Months	17 (17.3)	0.889
≥21 Months	16 (16.5)	

NSCLC: Non-small cell lung cancer; RCC: renal cell carcinoma. Bold values indicate statistical significance.

Table III. *Summary of the univariate analyses of potential prognostic pre-treatment factors including symptoms and seizures with respect to survival.*

Potential prognostic factor	At 6 months (%)	At 12 months (%)	At 18 months (%)	*p*-Value
Symptoms prior to SRS/FSRT				
No symptoms	71	53	35	0.181
Seizures alone	68	57	28	
Other symptoms alone	64	44	31	
Seizures + other symptoms	57	33	17	
Seizures prior to SRS/FSRT				
No seizures	65	46	32	0.431
Seizures	61	47	23	
Age at SRS/FSRT				
≤61 Years	70	50	30	0.447
≥62 Years	59	42	32	
Gender				
Female	66	47	34	0.447
Male	64	46	26	
Karnofsky performance score				
≤70%	47	32	16	**<0.001**
≥80%	73	54	37	
Type of primary tumor				
Breast cancer	78	58	37	0.059
NSCLC	66	46	31	
RCC	73	47	24	
Melanoma	64	49	36	
Other type	43	33	16	
Number of brain metastases				
One	67	50	30	0.229
Two or three	62	41	30	
Extra-cranial metastatic spread				
Absence	80	56	33	0.068
Presence	53	40	28	
Interval from first diagnosis of malignant disease to SRS/FSRT				
≤20 Months	64	42	24	0.055
≥21 Months	65	51	36	

SRS: Single-fraction radiosurgery; FSRT: Fractionated stereotactic radiotherapy; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; n.a.: not available. Bold value indicates statistical significance.

randomized trials emphasized that the addition of whole-brain radiotherapy is associated with a significant increase in cognitive deficits, physicians have become more hesitant regarding the combined approach and favor use of SRS/FSRT alone (9, 10). In the first trial, which was stopped after 58 patients, cognitive decline was observed in 24% and 96% of the patients at 4 months following SRS alone and following SRS supplemented by whole-brain radiotherapy, respectively ($p<0.001$) (9). In the second trial, which included 213 patients, cognitive decline at 3 months was observed in 64% of patients following SRS alone and in 92% of patients following SRS combined with whole-brain radiotherapy, respectively ($p<0.001$) (10). However, the rates of freedom from new or recurrent brain metastases at 1 year were significantly higher after the combined approach than after SRS alone. Intracerebral control rates were 27% after SRS alone *versus* 73% after SRS plus whole-brain radiotherapy in the first trial ($p<0.001$), and 15% *versus* 50% in the second ($p<0.001$) (9, 10). One has to be aware that a consequence of omitting whole-brain radiotherapy is worse control of intracerebral metastatic disease with associated symptoms, including seizures (11-13). About 20 years ago, the investigators of a trial of the Radiation Therapy Oncology Group (RTOG) reported that poor cognitive function was caused by intracerebral recurrence but by no other factor they had investigated (11). Similar findings were reported from prospective studies published a few years later (12, 13). Moreover, the risk of cognitive decline due to whole-brain radiotherapy can be significantly reduced with modern approaches including hippocampal-sparing radiotherapy and the drug memantine (18, 19). Memantine was shown to be safe and effective in the treatment of symptomatic Alzheimer's disease (20). In a randomized trial,

Table IV. *Multivariate analysis (Cox regression analysis) of survival.*

Potential prognostic factor	Risk ratio	95% Confidence interval	*p*-Value
Karnofsky performance score	2.08	1.45-2.95	**<0.001**
Type of primary tumor	1.07	1.00-1.14	**0.038**
Extra-cranial metastatic spread	1.34	0.94-1.94	0.107
Interval from first diagnosis of malignant disease to SRS or FSRT	1.66	1.16-2.38	**0.005**

SRS: Stereotactic radiosurgery; FSRT: Fractionated stereotactic radiotherapy. Bold values indicate statistical significance.

memantine when added to whole-brain radiotherapy led to a significant protraction of the time to post-treatment cognitive decline (p=0.01) (18). In another prospective study including a historical control group, whole-brain radiotherapy with a hippocampal-sparing technique resulted in a significant reduction of cognitive deficits from 30% to 7% (p<0.001) (19). Both procedures were also successfully used in combination (21). It is important to consider all pros and cons of the addition of whole-brain radiotherapy to SRS or FSRT for each individual patient with one to three brain metastases. A scoring system designed to predict the probability of developing new brain metastases after SRS or FSRT alone may support clinical decision making (14). Three risk groups were identified with 6-month rates of freedom from new brain metastases of 36%, 65% and 80%, respectively. Patients of the third group and many patients of the second group appear to be well treated with SRS or FSRT alone and may not require whole-brain radiotherapy.

The present study focused on those patients treated with SRS or FSRT alone. It was performed to contribute to the understanding of the role of seizures prior to SRS or FSRT in this group. The prevalence of pre-SRS/FSRT seizures was 16.9%, which was within the range of 12-35% reported from previous studies not particularly focusing on SRS/FSRT (15, 17, 22, 23). Furthermore, the current study aimed to identify risk factors for occurrence of seizures prior to SRS or FSRT. A significant association with seizures was shown for younger age (≤61 years). A similar finding was reported from a previous retrospective study including 286 patients with brain metastases who underwent neurosurgical resection (24). In addition, trends were found in the present study for associations between pre-SRS/FSRT seizures and NSCLC or absence of extra-cranial metastatic spread. Associations between the occurrence of seizures in patients with brain metastases and the type of primary tumor were previously described. In the study of Oberndorfer *et al.* and the review article of Ruda *et al.*, patients with lung cancer had the second highest prevalence of seizures (15, 25). Moreover, in the study of Wolpert *et al.*, the highest prevalence of pre-operative seizures was also found in patients with lung cancer (17). In contrast, a positive correlation between absence of extra-cranial metastatic spread and pre-SRS/FSRT seizures was not reported previously.

In this study, an association between pre-SRS/FSRT seizures and survival was not observed. This agrees with the literature, since a correlation was only described for patients with glioma but not for those with brain metastases (26). In contrast to pre-SRS/FSRT seizures, the performance status, the type of primary tumor and the interval from first diagnosis of the malignant disease to SRS or FSRT were independently associated with survival. Extra-cranial metastatic spread was significant on univariate analysis. These factors were previously identified in patients receiving SRS or FSRT for very few brain metastases (27-29). This showed consistency of our data with previous studies regarding survival. However, the retrospective nature of the data analyzed in this study needs to be considered during their interpretation.

In conclusion, the prevalence of seizures prior to SRS or FSRT in the present study was within the range of the reported data. Younger age, primary NSCLC and absence of extra-cranial spread appeared to be risk factors for the occurrence of seizures prior to SRS/FSRT. In contrast to other significant prognostic factors, the occurrence of pre-SRS/FSRT seizures was not associated with survival.

Conflicts of Interest

The Authors state that there are no conflicts of interest related to this study.

Authors' Contributions

All Authors participated in the design of the study. J.W. and D.R. provided the data. The data were analyzed by D.R. and S.E.S. and interpreted by all Authors. D.R. and S.E.S. drafted the article, which was reviewed and finally approved by all Authors.

Acknowledgements

As part of the project NorDigHealth project, the study achieved funding from the European Regional Development Fund through the Interreg Deutschland-Danmark program (087-1.1-18).

References

1 Khan M, Lin J, Liao G, Li R, Wang B, Xie G, Zheng J and Yuan Y: Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: Review and meta-analysis. Tumour Biol *39*: 1010428317702903, 2017. PMID: 28675121. DOI: 10.1177/1010428317702903

2 Tsao MN: Brain metastases: Advances over the decades. Ann Palliat Med *4*: 225-232, 2015. PMID: 26541403. DOI: 10.3978/j.issn.2224-5820.2015.09.01

3 Rades D, Dziggel L, Manig L, Janssen S, Khoa MT, Duong VN, Khiem VH and Schild SE: Predicting survival after whole-brain irradiation for cerebral metastases in patients with cancer of the bladder. In Vivo *32*: 633-636, 2018. PMID: 29695570. DOI: 10.21873/invivo.11285

4 Rades D, Dziggel and Schild SE: A specific survival score for patients receiving local therapy for single brain metastasis from a gynecological malignancy. In Vivo *32*: 825-828, 2018. PMID: 29936465. DOI: 10.21873/invivo.11314

5 Rades D, Blanck O, Khoa MT, Van Thai P, Hung NQ, Dziggel L and Schild SE: Validation of a survival score for patients receiving radiosurgery or fractionated stereotactic radiotherapy for 1 to 3 brain metastases. In Vivo *32*: 381-384, 2018. PMID: 29475924. DOI: 10.21873/invivo.11249

6 Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA and Chang EL: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol *2*: 210-225, 2012. PMID: 25925626. DOI: 10.1016/j.prro.2011.12.004

7 Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA and Young B: Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. JAMA *280*: 1485-1489, 1998. PMID: 9809728 DOI: 10.1001/jama.280.17.1485

8 Rades D, Veninga T, Hornung D, Wittkugel O, Schild SE and Gliemroth J: Single brain metastasis: Whole-brain irradiation plus either radiosurgery or neurosurgical resection. Cancer *118*: 1138-1144, 2012. PMID: 21761403. DOI: 10.1002/cncr.26379

9 Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH and Meyers CA: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol *10*: 1037-1044, 2009. PMID: 19801201. DOI: 10.1016/S1470-2045(09)70263-3

10 Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG 2nd, Deming R, Burri SH, Ménard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC and Asher AL: Effect of radiosurgery alone *vs*. radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. JAMA *316*: 401-409, 2016. PMID: 27458945. DOI: 10.1001/jama.2016.9839

11 Regine WF, Scott C, Murray K and Curran W: Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. Int J Radiat Oncol Biol Phys *51*: 711-717, 2001. PMID: 11597813. DOI: 10.1016/s0360-3016(01)01676-5

12 Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, Kunkler I, Caudrelier JM, Eisenberg PD, Meerwaldt J, Siemers R, Carrie C, Gaspar LE, Curran W, Phan SC, Miller RA and Renschler MF: Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: Results of a randomized phase III trial. J Clin Oncol *22*: 157-165, 2004. PMID: 14701778. DOI: 10.1200/JCO.2004.05.128

13 Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, Shioura H, Inomata T, Kunieda E, Hayakawa K, Nakagawa K, Kobashi G and Shirato H: Neurocognitive function of patients with brain metastasis who received either whole-brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys *68*: 1388-1395, 2007. PMID: 17674975. DOI: 10.1016/j.ijrobp.2007.03.048

14 Huttenlocher S, Dziggel L, Hornung D, Blanck O, Schild SE and Rades D: A new prognostic instrument to predict the probability of developing new cerebral metastases after radiosurgery alone. Radiat Oncol *9*: 215, 2014. PMID: 25240823. DOI: 10.1186/1748-717X-9-215

15 Rudà R, Mo F and Pellerino A: Epilepsy in brain metastasis: An emerging entity. Curr Treat Options Neurol *22*: 6, 2020. PMID: 32034533. DOI: 10.1007/s11940-020-0613-y

16 Wu A, Weingart JD, Gallia GL, Lim M, Brem H, Bettegowda C and Chaichana KL: Risk factors for preoperative seizures and loss of seizure control in patients undergoing surgery for metastatic brain tumors. World Neurosurg *104*: 120-128, 2017. PMID: 28512046. DOI: 10.1016/j.wneu.2017.05.028

17 Wolpert F, Lareida A, Terziev R, Grossenbacher B, Neidert MC, Roth P, Poryazova R, Imbach L, Le Rhun E and Weller M. Risk factors for the development of epilepsy in patients with brain metastasis. Neuro Oncol pii: noz172, 2019. PMID: 31498867. DOI: 10.1093/neuonc/noz172

18 Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, Choucair A, Fox S, Suh JH, Roberge D, Kavadi V, Bentzen SM, Mehta MP and Watkins-Bruner D; Radiation Therapy Oncology Group (RTOG): Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. Neuro Oncol *15*: 1429-1437, 2013. PMID: 23956241. DOI: 10.1093/neuonc/not114

19 Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L and Mehta MP: Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. J Clin Oncol *32*: 3810-3816, 2014. PMID: 25349290. DOI: 10.1200/JCO.2014.57.2909

20 Rogawski MA and Wenk GL: The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev *9*: 275-308, 2003. PMID: 14530799. DOI: 10.1111/j.1527-3458.2003.tb00254.x

21 Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, Bovi JA, Robinson C, Konski A, Khuntia D, Grosshans D, Benzinger TLS, Bruner D, Gilbert MR, Roberge D, Kundapur V, Devisetty K, Shah S, Usuki K, Anderson BM, Stea B, Yoon H, Li J, Laack NN, Kruser TJ, Chmura SJ, Shi W, Deshmukh S, Mehta MP and Kachnic LA; for NRG Oncology: Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology

CC001. J Clin Oncol *38*: JCO1902767, 2020. PMID: 32058845. DOI: 10.1200/JCO.19.02767

22 Rostami R, Mittal S, Rostami P, Tavassoli F and Jabbari B: Brain metastasis in breast cancer: A comprehensive literature review. J Neurooncol *127*: 407-414, 2016. PMID: 26909695. DOI: 10.1007/s11060-016-2075-3

23 Chan V, Sahgal A, Egeto P, Schweizer T and Das S: Incidence of seizure in adult patients with intracranial metastatic disease. J Neurooncol *131*: 619-624, 2017. PMID: 27878505. DOI: 10.1007/s11060-016-2335-2

24 Puri PR, Johannsson B, Seyedi JF, Halle B, Schulz M, Pedersen CB, Kristensen BW and Poulsen FR: The risk of developing seizures before and after surgery for brain metastases. Clin Neurol Neurosurg *193*: 105779, 2020. PMID: 32200217. DOI: 10.1016/j.clineuro.2020.105779

25 Oberndorfer S, Schmal T, Lahrmann H, Urbanits S, Lindner K and Grisold W: The frequency of seizures in patients with primary brain tumors or cerebral metastases. An evaluation from the Ludwig Boltzmann Institute of Neuro-Oncology and the Department of Neurology, Kaiser Franz Josef Hospital, Vienna. Wien Klin Wochenschr *114*: 911-916, 2002. PMID: 12528323.

26 Lote K, Stenwig AE, Skullerud K and Hirschberg H: Prevalence and prognostic significance of epilepsy in patients with gliomas. Eur J Cancer *34*: 98-102, 1998. PMID: 9624245. DOI: 10.1016/s0959-8049(97)00374-2

27 Rades D, Huttenlocher S, Dziggel L, Blanck O, Hornung D, Mai KT, Ngo TT, Van Pham T, Schild S: A new tool to predict survival after radiosurgery alone for newly diagnosed cerebral metastases. Asian Pac J Cancer Prev *16*: 2967-2970, 2015. PMID: 25854390. DOI: 10.7314/apjcp.2015.16.7.2967

28 Rades D, Janssen S, Dziggel L, Blanck O, Bajrovic A, Veninga T and Schild SE: A matched-pair study comparing whole-brain irradiation alone to radiosurgery or fractionated stereotactic radiotherapy alone in patients irradiated for up to three brain metastases. BMC Cancer *17*: 30, 2017. PMID: 28061768. DOI: 10.1186/s12885-016-2989-3

29 Weltman E, Salvajoli JV, Brandt RA, de Morais Hanriot R, Prisco FE, Cruz JC, de Oliveira Borges SR and Wajsbrot DB: Radiosurgery for brain metastases: A score index for predicting prognosis. Int J Radiat Oncol Biol Phys *46*: 1155-1161, 2000. PMID: 10725626. DOI: 10.1016/s0360-3016(99)00549-0

Received April 25, 2020
Revised May 13, 2020
Accepted May 15, 2020