Elderly Patients With Single Brain Metastasis – Overall Survival After Surgery Plus Whole-Brain Irradiation and a Radiation Boost

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Abstract. *Background/Aim:* Elderly patients with a single brain metastasis likely benefit from personalized treatment protocols. To add to treatment personalization, a survival score was generated for these patients. *Patients and Methods:* This retrospective study included 36 elderly patients, each with a single brain metastasis, who received surgery followed by whole-brain irradiation and a radiation boost. Six pre-treatment characteristics were evaluated regarding survival, namely age, gender, Karnofsky performance score (KPS), type of primary tumor, non-cerebral metastasis and interval from diagnosis of the neoplasm until surgery. *Results:* When applying the Cox regression model, KPS ($p=0.005$) and tumor type ($p=0.018$) were significant and incorporated in the score. Based on 12-month survival probabilities, three groups of 6-9 ($n=5$), 10-11 ($n=15$) and 14-19 points ($n=16$) were formed, with 12-month survival rates of 0%, 33% and 100%, respectively ($p<0.0001$). *Conclusion:* A survival score was generated specifically for elderly patients with a single brain metastasis that can improve personalization of their treatment.

Patients with a single brain metastasis are less common than patients with multiple lesions (1). If the brain lesion is surgically accessible and the patients are medically operable, they may be candidates for resection (1-4). Outcomes of patients with a single brain metastasis may be further improved with post-operative radiation therapy (5). A

previous study of patients aged ≥ 65 years with one or two brain metastases compared four treatment protocols, namely whole-brain irradiation (WBI) alone, radiosurgery alone, surgery followed by WBI and surgery followed by WBI plus a radiation boost to the resection cavity (6). The combined approach of surgery followed by WBI plus a boost achieved the best outcomes at 1 year in terms of significantly better survival, local control of the resected lesions and overall cerebral control. Thus, surgery followed by WBI plus a boost appeared preferable for elderly patients with one or two brain metastases. However, for many of these patients an invasive procedure such as brain surgery can be burdensome, particularly if they are impaired with underlying diseases. Moreover, in the previous study, the differences between the four treatments were less prominent at 6 months than at 1 year (6). Considering these results, an aggressive approach such as surgery followed by WBI plus a boost appeared more appropriate for longer-term survivors with comparably little co-morbidity. Therefore, it is important for the treating physicians to identify prior to the start of treatment a) patients who will likely live long enough to benefit from an aggressive multidisciplinary regimen and b) those patients who may not benefit. This study aimed to provide a score to support the estimation of a patient's survival prognosis and, thereby, contribute to the identification of patients who will likely live long enough to gain adequate benefit from such an aggressive regimen.

Patients and Methods

This retrospective study included 36 patients, each with a single brain metastasis, who were at least 65 years of age and had received surgery (resection of the metastasis) followed by WBI and a radiation boost to the metastatic site. The study was approved by the Ethics Committee of the University of Lübeck. The goal of this study was the development of a score that allowed the estimation of the 12-month survival. Six pre-treatment characteristics (Table I) were evaluated with respect to survival, including age (≤ 67 vs. ≥ 68 years, median: 67 years), gender, Karnofsky performance score

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Key Words: Elderly patients, single brain metastasis, surgery, whole-brain irradiation, radiation boost, overall survival.

Table I. Patient, tumor and treatment characteristics.

Characteristic	Number of patients (%)
Age	
≤67 Years	19 (53)
≥68 Years	17 (47)
Gender	
Female	11 (31)
Male	25 (69)
KPS	
70-80	21 (58)
90-100	15 (42)
Type of primary tumor	
Breast cancer	5 (14)
NSCLC	14 (39)
RCC/melanoma	7 (19)
GI-cancers	6 (17)
Other types	4 (11)
Non-cerebral metastasis	
Yes	6 (17)
No	30 (83)
Interval from first diagnosis of neoplasm until surgery	
≤21 Months	18 (50)
≥22 Months	18 (50)

KPS: Karnofsky performance score; NSCLC: non-small cell lung cancer; RCC: renal-cell carcinoma; GI: gastrointestinal.

(KPS 70-80 vs. 90-100, median: 80), type of primary tumor [breast cancer vs. non-small cell lung cancer (NSCLC) vs. renal-cell carcinoma (RCC)/melanoma vs. gastrointestinal cancers vs. other tumor types], non-cerebral metastasis (yes vs. no) and interval from first diagnosis of the neoplasm until surgery of brain metastasis (≤21 vs. ≥22 months, median: 21.5 months). Radiation therapy regimens included 10×3 Gy of WBI followed by a boost of 5×3 Gy (*n*=16), 20×2 Gy of WBI followed by a boost of 5×2 Gy (*n*=12), 10×3 Gy of WBI followed by a boost of 3×3 Gy (*n*=6), 10×3 Gy of WBI followed by a boost of 10×2 Gy (*n*=1) and 14×2.5 Gy plus a simultaneous integrated boost of 7 Gy (*n*=1).

Time to death was referenced from the day of surgery. The characteristics that proved to be significantly (*p*<0.05) associated with survival or showed a trend (*p*<0.10) for such an association on univariate analysis (Kaplan-Meier method and log-rank test), were analyzed for independence using a Cox regression model. Characteristics achieving significance (*p*<0.05) in the Cox regression analysis were incorporated in the newly developed score. Initially, scoring points for each characteristic were devised by dividing the 12-month survival rates in percentage by 10. Afterwards, these scoring points were added for each individual patient.

Results

Median follow up was 13.5 months (range=1-66 months) in all 36 patients and 16.5 months (range=7-66 months) in those 10 patients alive at their last contact.

The median survival time of all 36 patients was 17 months, and the 6- and 12-month survival rates were 75%

Table II. Six- and 12-month survival rates of the evaluated characteristics.

Characteristic	6 months (%)	12 months (%)	<i>p</i> -Value
Age			
≤67 Years	79	62	0.122
≥68 Years	71	53	
Gender			
Female	73	62	0.736
Male	76	56	
KPS			
70-80	67	38	0.006
90-100	87	87	
Type of primary tumor			
Breast cancer	80	60	0.061
NSCLC	79	57	
RCC/melanoma	100	100	
GI-cancers	50	17	
Other types	50	50	
Non-cerebral metastasis			
Yes	50	25	0.086
No	80	63	
Interval from first diagnosis of neoplasm until surgery			
≤21 Months	61	44	0.273
≥22 Months	89	71	

KPS: Karnofsky performance score; NSCLC: non-small cell lung cancer; RCC: renal-cell carcinoma; GI: gastrointestinal; bold *p*-value is significant.

Table III. Independent predictors of 12-month survival and related scoring points.

Characteristic	12-month survival (%)	Scoring points
KPS		
70-80	38	4
90-100	87	9
Type of primary tumor		
Breast cancer	60	6
NSCLC	57	6
RCC/melanoma	100	10
GI-cancers	17	2
Other types	50	5

KPS: Karnofsky performance score; NSCLC: non-small cell lung cancer; RCC: renal-cell carcinoma; GI: gastrointestinal.

and 58%. When the univariate analyses were performed (Table II), a KPS of 90-100 (*p*=0.006) was significantly associated with a more favorable survival. In addition, a trend was found for comparably favorable types of primary tumor, namely breast cancer, NSCLC and RCC/melanoma, (*p*=0.061) and absence of non-cerebral metastasis (*p*=0.086). When applying the Cox regression model, KPS of 90-100 [risk ratio (RR)=3.44, 95% confidence interval (CI)=1.44-

Figure 1. Survival rates of the different scoring points at 12 months following surgery.

9.09, $p=0.005$] and favourable types of primary tumor ($RR=1.22$, $95\%CI=1.04-1.43$, $p=0.018$) were significant, whereas absence of non-cerebral metastasis ($RR=2.39$, $95\%CI=0.65-7.26$, $p=0.176$) did not achieve significance. Thus, KPS and type of primary tumor were incorporated in the score as described above.

The scoring points of these two characteristics are shown in Table III. When applying this methodology, individual patients received scores that ranged between 6 and 19 points (Figure 1). Based on 12-month survival probabilities, three survival groups were formed: 6-9 points ($n=5$), 10-11 points ($n=15$) and 14-19 points ($n=16$). The 12-month survival rates of these groups were 0%, 33% and 100%, respectively (Figure 2, $p<0.0001$).

Discussion

Several treatment options exist for elderly patients with a single brain metastasis including WBI alone, radiosurgery alone and surgery followed by WBI with or without a radiation boost to the resection cavity (1, 6). A retrospective study of 164 patients with one or two brain metastases compared these treatments according to the survival, intracerebral control and local control they achieved (6). At 12 months, the highest survival rate was observed after surgery plus WBI and a boost, *i.e.* 61% compared to 40% after radiosurgery alone, 27% after surgery plus WBI and 13% after WBI alone ($p<0.001$). Surgery plus WBI and a boost was also significantly superior to the other regimens with respect to 12-month intracerebral control (79% vs. 55%, 36% and 17%, respectively, $p<0.001$) and local control of the resected lesions (84% vs. 68%, 43% and 19%, respectively, $p<0.001$). At 6 months, the differences between the four regimens were less prominent (6). For example, the 6-month rates of survival, intracerebral control and local control were 78%, 82% and 86%, respectively, after surgery plus WBI and a boost compared to 56%, 48% and 53%, respectively, after

Figure 2. Kaplan-Meier curves of the patient-groups achieving 6-9 points ($n=5$), 10-11 points ($n=15$) and 14-19 points ($n=16$), respectively.

WBI alone. Thus, patients surviving for ≥ 12 months had a greater benefit from the most aggressive approach (surgery followed by WBI and a radiation boost) than patients surviving for only 6 months. Since such an aggressive treatment program can be very stressful for elderly patients, the potential benefits should be carefully weighed against potential toxicities and complications. The benefit-risk assessment should also take into account a patient's survival prognosis, since benefit increases with lifetime. Therefore, it is important to accurately estimate a patient's remaining lifespan before considering an aggressive treatment protocol.

This study created a new survival score for elderly patients with a single brain metastasis, developed in a cohort treated with surgery plus WBI and a radiation boost. Based on the independent prognostic factors, KPS and type of primary tumor, we designed three groups with different 12-month survival probabilities. In the 6-9 points group, no patient survived as long as 12 months following surgery, and only 40% of these patients survived for 6 months. Therefore, these

patients appeared less than ideal candidates for an aggressive treatment including neurosurgical resection (6). They may be better treated with radiosurgery alone that achieved the second-best results regarding survival, intracerebral control and local control in the previous study (6). Patients of the 10-11 points group had 6- and 12-month survival rates of 60% and 33%, respectively. Since the 12-month survival rate was, although better than in the 6-9 points group, also not convincingly long, surgery plus WBI and a boost may be limited to selected patients. The majority of these patients may be considered for radiosurgery alone. When wishing to combine radiosurgery with novel targeted therapies, which is becoming increasingly popular for younger patients, one should be aware that these new systemic drugs can lead to severe adverse events particularly in elderly patients (7, 8).

In contrast to these two groups (5-9 points and 10-11 points), patients of the 14-19 points group had an excellent long-term survival with 12-month and 24-month survival rates of 100% and 82%, respectively (Figure 2). These patients appear to benefit from surgery plus WBI and a radiation boost in terms of increased survival, intracerebral control and local control (6). They may also be considered for WBI plus radiosurgery, which provided similar 1-year outcomes as surgery plus WBI and a boost in a matched-pair study of 94 patients with one or two brain metastases and a matched-pair study of 92 patients of any age with a single lesion (2, 9). Studies comparing these two treatments in elderly patients alone are lacking.

The role of WBI in addition to a local therapy is currently under debate. Two older studies, a randomized trial ($n=95$) and a retrospective study ($n=85$) compared surgical resection alone to resection plus WBI for a single brain metastasis (3, 4). In the randomized trial, WBI led to increased 1-year local control (90% vs. 54%, $p<0.001$) and intracerebral control (82% vs. 30%, $p<0.001$) but not survival (median 11 months in both groups) (3). In the retrospective study, WBI resulted in increased 1-year local control (79% vs. 15%, $p<0.05$) and survival (median 23 vs. 11.5 months, $p<0.05$) (4). More recently, two randomized trials demonstrated that WBI when added to radiosurgery resulted in a significantly higher rate of cognitive decline after a few months (10, 11). However, in both trials, significantly more intracerebral recurrences were found after 12 months in the radiosurgery alone arm. One has to be aware that intracerebral progression can also be associated with impairment of cognitive function, as well as the need for further therapy (12). Patients who have a considerable risk of developing an intracerebral recurrence after radiosurgery alone should be considered for upfront WBI (13). If a patient is assigned to a local therapy plus WBI, the risk of cognitive decline can be significantly reduced with WBI-techniques sparing the hippocampal areas and with administration of memantine, which is normally used for dementia and Alzheimer's disease (14-16). These options

should be considered particularly for patients achieving 14-19 points in our study, who are assigned to surgery plus WBI and a boost. When following the recommendations given in this article, the retrospective nature of the study with its risk of bias should be kept in mind.

In summary, a survival score was generated specifically for elderly patients with a single brain metastasis. This new score can improve personalization of their treatment by identifying patients who may be helped with an aggressive treatment protocol such as surgical resection followed by WBI and a radiation boost to the resection cavity.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

D.R., T.N. and S.E.S. designed the study. T.N. and D.R. collected or provided data that were analyzed by D.R. and S.E.S. The draft of the article was written by D.R. and S.E.S. and subsequently reviewed and approved by all Authors.

References

- 1 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
- 2 Rades D, Kueter JD, Meyners T, Pluemer A, Veninga T, Gliemroth J and Schild SE: Single brain metastasis: resection followed by whole-brain irradiation and a boost to the metastatic site compared to whole-brain irradiation plus radiosurgery. *Clin Neurol Neurosurg* 114: 326-330, 2012. PMID: 22152784. DOI: 10.1016/j.clineuro.2011.10.042
- 3 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
- 4 Smalley SR, Schray MF, Laws ER Jr and O'Fallon JR: Adjuvant radiation therapy after surgical resection of solitary brain metastasis: association with pattern of failure and survival. *Int J Radiat Oncol Biol Phys* 13: 1611-1616, 1987. PMID: 3117742. DOI: 10.1016/0360-3016(87)90154-4
- 5 Rades D, Kueter JD, Gliemroth J, Veninga T, Pluemer A and Schild SE: Resection plus whole-brain irradiation versus resection plus whole-brain irradiation plus boost for the treatment of single brain metastasis. *Strahlenther Onkol* 188: 143-147, 2012. PMID: 22234538. DOI: 10.1007/s00066-011-0024-9
- 6 Rades D, Pluemer A, Veninga T and Schild SE: Comparison of different treatment approaches for one to two brain metastases in elderly patients. *Strahlenther Onkol* 184: 565-571, 2008. PMID: 19016014. DOI: 10.1007/s00066-008-1908-1

- 7 Stera S, Balermipas P, Blanck O, Wolff R, Wurster S, Baumann R, Szücs M, Loutfi-Krauss B, Wilhelm ML, Seifert V, Rades D, Rödel C, Dunst J, Hildebrandt G, Arnold A, Meissner M and Kähler KC: Stereotactic radiosurgery combined with immune checkpoint inhibitors or kinase inhibitors for patients with multiple brain metastases of malignant melanoma. *Melanoma Res* 29: 187-195, 2019. PMID: 30802230. DOI: 10.1097/CMR.0000000000000542
- 8 Petrelli F, De Stefani A, Trevisan F, Parati C, Inno A, Merelli B, Ghidini M, Bruschi L, Vitali E, Cabiddu M, Borgonovo K, Ghilardi M, Barni S and Ghidini A: Combination of radiotherapy and immunotherapy for brain metastases: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 144: 102830, 2019. PMID: 31733443. DOI: 10.1016/j.critrevonc.2019.102830
- 9 Rades D, Kueter JD, Pluemer A, Veninga T and Schild SE: A matched-pair analysis comparing whole-brain radiotherapy plus stereotactic radiosurgery *versus* surgery plus whole-brain radiotherapy and a boost to the metastatic site for one or two brain metastases. *Int J Radiat Oncol Biol Phys* 73: 1077-1081, 2009. PMID: 18707817. DOI: 10.1016/j.ijrobp.2008.05.035
- 10 Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornuth 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
- 11 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
- 12 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
- 13 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
- 14 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
- 15 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
- 16 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

Received February 19, 2020

Revised March 25, 2020

Accepted March 26, 2020