

Patterns of Treatment and Outcome in Patients With 20 or More Brain Metastases

CARSTEN NIEDER^{1,2}, ROSALBA YOBUTA¹ and BÅRD MANNÅKER¹

¹Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway;

²Department of Clinical Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway

Abstract. *Background/Aim:* The aim of this study was to analyze the patterns of treatment and outcomes in patients with a large number of brain metastases, arbitrarily defined as 20 or more lesions. These patients are typically excluded from studies of focal brain treatment, e.g., surgery or radiosurgery, and might have a limited prognosis. *Patients and Methods:* This was a retrospective single-institution analysis. Overall, 11 patients were identified from a prospectively maintained database. *Results:* Ten patients had received active treatment (9 whole-brain radiotherapy, 7 systemic therapy). Median survival was 5.0 months without long-term survival beyond 13 months. Patients with better performance status had numerically longer survival, however we did not identify baseline parameters with a significant impact on survival. *Conclusion:* While long-term survival was not observed in this small study, most patients survived long enough to experience symptomatic improvement from whole-brain radiotherapy. Therefore, we recommend multidisciplinary assessment of the patients' prognosis and systemic treatment options, and initiation of whole-brain radiotherapy if survival is not limited to 1-2 months.

Advances in diagnostic imaging have facilitated detection of small intracranial lesions (1-3) and thus resulted in decreasing numbers of patients who present with 1-3 brain metastases from solid extracranial primary tumors, e.g., lung, breast, kidney cancer or malignant melanoma (4). Many patients with 1-3 brain metastases are considered adequate candidates for surgery and/or radiosurgery (SRS) (5-8). Technically, it is also

feasible to irradiate more than three lesions with SRS, however there is no consensus about the maximum number of metastases that qualify for focal treatment, as opposed to whole-brain radiotherapy (WBRT) (9). Some groups have offered SRS to selected patients with 4-10 brain metastases, others also to those with even more lesions (10-13). With increasing lesion number, durable brain control is difficult to achieve. There is scarce data about the group of patients with a large number of brain metastases, and therefore we analyzed our Institution's prospectively maintained database. We arbitrarily decided to focus on patients with 20 or more brain metastases, a group which typically is excluded from studies of SRS or other focal treatments.

Materials and Methods

Patients and treatment. A retrospective study of patients with 20 or more synchronous or metachronous parenchymal brain metastases from histologically verified extracranial primary tumors treated at our hospital was performed. Treatment was individualized and consisted of WBRT, combined WBRT with systemic therapy or best supportive care (BSC). Systemic treatment was usually prescribed as judged appropriate by the patients' medical oncologists. The patients were treated between January 01, 2007 and December 31, 2017 and identified from a previously described database (14, 15). Brain magnetic resonance imaging was performed to assess the number of intracranial metastases and to exclude leptomeningeal disease.

Statistical methods. Overall survival (time to death) from the first day of radiotherapy or, in case of BSC, from imaging diagnosis was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 24, IBM Corp., Armonk, NY, USA). Date of death was known in all patients. Statistical significance was defined as $p < 0.05$ throughout this study in two-sided tests.

Results

Patient characteristics. Overall, 11 patients were identified from the database, corresponding to less than 5% of patients. Four patients had primary malignant melanoma and small cell lung cancer (SCLC), respectively. Non-small cell lung

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Correspondence to: Dr. Carsten Nieder, Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway. Tel: +47 75578449, Fax: +47 75534975, e-mail: carsten.nieder@nlsh.no

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Table I. Patient characteristics.

Diagnosis	Time interval in months	Primary tumor controlled	Extracranial metastases	Neurologic symptoms	Response to steroids	Treatment	Systemic therapy	KPS	Diameter of largest lesion in cm	Number of lesions	Age in years	Survival in months	Cause of death
HER2+ breast cancer	10	Yes	Hep, oss	Yes	Yes	WBRT 30 Gy	Trastuzumab	70	1.9	50	50	10.2	Impossible to determine
Adeno NSCLC	0	No	Hep	Yes	No	1 cycle CTx, died before WBRT	No	70	2.6	20	72	1.5	Likely neurologic
Melanoma	156	Yes	Pul, lym	Yes	No	WBRT 30 Gy	Dabrafenib + Trametinib	70	3.2	24	49	8.3	Neurologic
Melanoma	33	Yes	Pul, adr, oth	Yes	No	WBRT 30 Gy	No	60	3.0	21	67	2.0	Likely neurologic
Adeno NSCLC	0	Yes	Hep, oss	No	NA	WBRT 30 Gy	CTx	60	1.1	50	69	12.6	Likely non-neurologic
SCLC	0	No	No	No	NA	4 cycles CTx, then WBRT 30 Gy	CTx	90	1.8	20	67	10.5	Likely non-neurologic
Melanoma	28	Yes	Hep, pul, oss	Yes	Yes	WBRT 40 Gy with temozolomide	CTx	80	3.6	25	40	2.3	Impossible to determine
SCLC	6	Yes	Hep, oss	Yes	?	WBRT 30 Gy	No	60	1.0	36	72	5.0	Likely non-neurologic
Melanoma	120	No	Pul, adr, oth	Yes	Yes	WBRT 36 Gy	CTx	60	3.0	23	64	5.5	Impossible to determine
SCLC	6	Yes	Hep, adr, oss	Yes	No	WBRT 30 Gy	No	30	1.3	50	51	2.0	Non-neurologic
SCLC	4	No	Hep, adr, oth	Yes	Yes	Converted to BSC	No	60	1.5	25	75	1.2	Likely non-neurologic

NSCLC: Non-small cell lung cancer; SCLC: small cell lung cancer; hep: hepatic; oss: osseous; pul: pulmonary; lym: lymph nodes; adr: adrenal gland; oth: others; NA: not applicable; CTx: chemotherapy; WBRT: whole-brain radiotherapy; BSC: best supportive care; KPS: Karnofsky performance status.

cancer (NSCLC) was present in 2 patients, while one had a diagnosis of breast cancer. Only one patient had brain-only dissemination and two had Karnofsky performance status (KPS) >70. Further patient characteristics are shown in Table I, while imaging findings are displayed in Figure 1.

Treatment. Ten patients received active treatment, and one who initially was referred to WBRT was converted to BSC due to rapid deterioration of his KPS. Overall, nine patients received WBRT, commonly 10 fractions of 3 Gy. Seven patients received systemic therapy after their brain metastases diagnosis.

Survival. Median overall survival of all 11 patients was 5.0 months (range=1.2-12.6 months). In the absence of systemic treatment, median survival was 2.0 months. If KPS was 70 or better, median survival was 8.3 months compared to 3.5 months if KPS was <70 ($p=0.78$). Age, size of the largest lesion, time interval between primary diagnosis and brain metastases, and other baseline variables were not significantly associated with survival either.

Discussion

We performed a retrospective study of patients with brain metastases and presumably limited prognosis due to the fact that the presence of many lesions rendered these patients ineligible for surgery or SRS, at least according to our institution's policy. SRS has recently gained increasing acceptance also in patients with more than just 1-2 brain metastases, because the probability of local lesion control is much higher after SRS than after WBRT, simply as a function of the higher ablative radiation dose delivered. In contrast, development of distant brain failure often results in need for further SRS or WBRT (9, 10). Besides local brain control, a variety of other factors that can be combined in prognostic scores are crucial determinants of long-term survival (5, 6, 8, 16, 17).

Recent studies of SRS reported median numbers of metastases of 2 (range=1-17 metastases) (12) and 5 (range=4-23 metastases) (11), reflecting the different approaches chosen in different institutions. The latter study

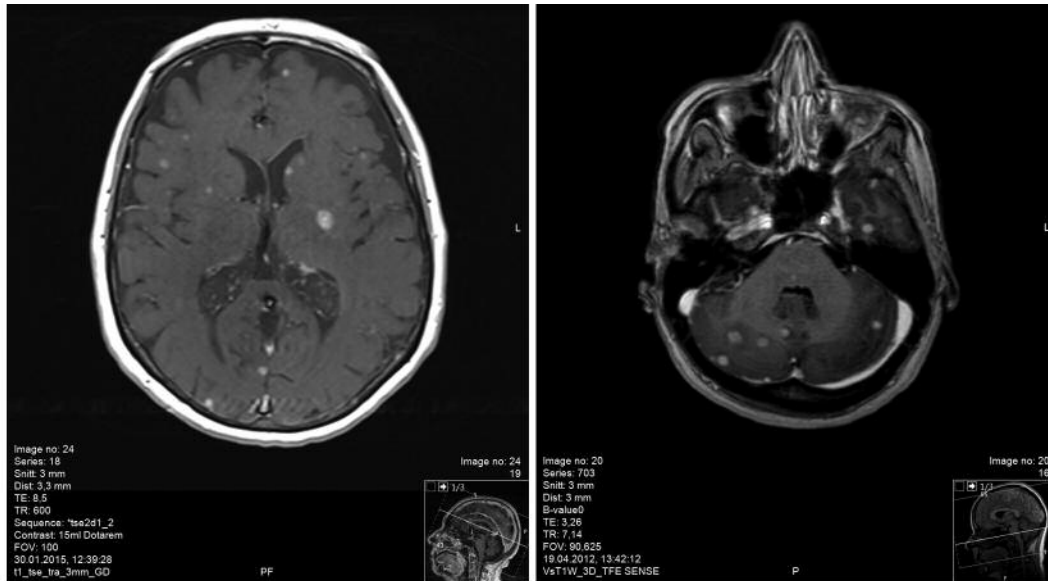


Figure 1. Magnetic resonance imaging scans of two study patients who presented with multiple contrast-enhancing brain metastases (examples of infra- (patient 7) and supratentorial (patient 5) disease extent, respectively).

of patients with at least four metastases reported better survival with smaller total tumor volume (11). Ali *et al.* (13) analysed more than 5,000 patients. The maximum number of metastases was not reported. The median survival of patients with >10 brain metastases was lower than that of those with 2-10 lesions (6.3 months *vs.* 5.5 months, $p=0.025$). When lesion number was modelled as a continuous variable rather than using the cut-off, they observed a step-wise 4% increase in the hazard of death for every increment of 6-7 brain metastases ($p<0.001$). In our study, median survival was 5.0 months and none of the patients had ever received SRS. Overall 5 patients survived for less than 3 months, emphasizing that careful selection is needed. Poor KPS and ineligibility for systemic therapy should be taken into consideration when deciding about WBRT. Since almost all patients had extracranial metastases, long-term survival is not purely a function of optimal local control in the brain. None of our patients had miliary brain metastases from EGFR mutated NSCLC, a special entity that may respond to targeted systemic therapy (18).

Chang *et al.* evaluated 323 patients who underwent SRS for metastatic brain lesions (19). Patients were divided into 4 groups according to the number of lesions visible on magnetic resonance (MR) images: Group 1, 1-5 lesions; Group 2, 6-10 lesions; Group 3, 11-15 lesions; and Group 4, >15 lesions. The overall median survival time after SRS was 10 months. The median survival time of each group was as follows: Group 1, 10 months; Group 2, 10 months; Group 3, 13 months; and Group 4, 8 months. There was no statistical

difference between survival times after SRS ($p=0.554$), although the probability of development of new lesions in the brain was greater in Group 4 ($p=0.014$). Inter-study comparison of the survival outcomes is difficult, because Asian populations often include larger proportions of NSCLC patients with actionable mutations and also because patients managed with BSC were not included.

Limitations of the present study include the limited number of patients, statistical power of subgroup analyses, and its retrospective design. In many cases we were unable to firmly establish neurologic *vs.* other causes of death. Furthermore, quality of life data confirming the clinical benefit of WBRT and its potential neurocognitive impact were not available. A currently recruiting study is expected to provide relevant data in this context (20). CAR-Study B is a prospective randomized trial comparing cognitive outcome after SRS or WBRT in patients with 11-20 newly diagnosed brain metastases on a contrast-enhanced MRI scan, KPS ≥ 70 and life expectancy of at least 3 months. Secondary endpoints include overall survival, local control, development of new brain metastases, cognitive functioning over time, quality of life, depression, anxiety and fatigue. Assessments are scheduled at baseline and at 3, 6, 9, 12 and 15 months after treatment.

Conclusion

While long-term survival was not observed in this small study, most patients survived long enough to experience

symptomatic improvement from WBRT. Therefore, we recommend multidisciplinary assessment of the patients' prognosis and systemic treatment options, and initiation of WBRT if survival is not limited to 1-2 months.

Conflicts of Interest

The Authors declare that they have no competing interests.

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