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Original Investigation

Whole Brain Radiotherapy Plus Conventional Boost in Non-Small Cell Lung Cancer Patients with Brain Metastasis: A Retrospective Analysis of Overall Survival

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ABSTRACT

AIM: We reviewed and retrospectively evaluated clinical characteristics and treatment outcomes of non-small cell lung cancer (NSCLC) patients with brain metastasis, who were treated by whole brain radiotherapy with a conventional boost at a single institution.

MATERIAL and METHODS: A total of 296 patients diagnosed with NSCLC with brain metastasis and referred to our clinic for radiotherapy between 2000 and 2017 were included in this retrospective study.

RESULTS: The median age was 60.8 ± 12.1 years, with a range of 21–85 years. The estimated median survival time for all patients was 7.81 ± 0.66 months (95% CI: 6.52–9.11). The one-year survival, two-year survival and three-year survival rates were 18.8%, 5.8% and 2.9%, respectively. The median survival of patients with solitary brain metastasis who received 45 Gy radiotherapy was 14.70 ± 2.80 months (95% CI: 9.20–20.20). These patients had 6 and 12 months survival rates of 65.4% and 42.6%, respectively. The median survival time of patients with solitary brain metastasis who received > 45 Gy radiotherapywas 13.86 ± 2.56 months (95% CI: 8.08–18.02). These patients had 6 and 12 months survival rates of 66.2% and 27.2%, respectively. There was no significant difference between the two groups (p=0.321). The median survival duration of patients under 65 years was 9.65 ± 1.02 months. The median survival time of patients aged 65 years and overwas 5.15 ± 0.51 months. There was a statistically significant difference in the median survival rates between the groups (p<0.001).

CONCLUSION: Patients with solitary metastasis or single metastases tolerated whole brain radiotherapy with a conventional boost. Although the overall survival rates were numerically better in the high dose RT group, the difference was not statistically significant. Prospective studies with a larger sample size are needed to consolidate our results.

KEYWORDS: Non-small cell lung cancer, Brain metastases, Radiotherapy

INTRODUCTION

Brain metastases are the most common type of intracranial tumours (8 times more common than primary brain tumours) and are significantly relevant in patients with cancer. Brain metastases are a widespread complication of systemic cancers and occur in one out of three cancer patients (20). Probably due to improvements in overall survival, the incidence of brain metastasis is on the rise. Primary cancers such as breast cancer, lung cancer, melanoma and renal cell carcinoma are most likely to metastasise to the brain.

Lung cancer is a significant source of brain metastasis. Approximately 34%–64% of patients with non-small cell lung cancer (NSCLC) develop brain metastasis. Of these patients, 10%–20% present with brain metastases at the time of diagnosis (7,12).

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The term solitary brain metastasis describes the only known metastasis of a tumour in the whole body that localises in the central nervous system. A single brain metastasis is defined as a single cerebral metastasis with additional metastases in other organ systems (25).

Treatment of brain metastases is a multidisciplinary approach. Treatment options include surgery, radiotherapy and chemotherapy. Therefore, close cooperation is needed between medical oncologists, neurosurgeons and radiation oncologists. Surgery plays a major role in the local control of metastatic disease. It is the most commonly accepted treatment option for local control in cases of oligometastases. The term 'oligometastasis' describes the presence of 3 or more metastatic tumours at any site. After metastasectomy, adjuvant treatment options include whole brain radiotherapy (WBRT), local radiotherapy (RT) to the tumour bed or observation with best supportive care. Traditionally, WBRT has been commonly performed, with a typical dose of 30 Gy in 10 fractions. Regardless, since prolonged local control is unusual, WBRT mostly has a palliative effect, including in patients with multiple brain metastases. However, dose escalation approaches based on standard radiation therapy techniques have raised concerns about quality of life and neurocognitive impairment, thereby restricting this field of research. Simultaneous irradiation of the brain and metastases at various doses may be useful in terms of local control and overall survival (OS) in selected patients (5). With advances in imaging and techniques for stereotactic radiosurgery (SRS), radiation metastasectomy is becoming more common (3).

In this study, we aimed to investigate the effect of dose escalation on the OS in NSCLC patients with brain metastasis.

MATERIAL and METHODS

This retrospective clinical study was conducted with permission from the Ethics Committee at the Karadeniz Technical University Faculty of Medicine (2017-188). A total of 296 NSCLC patients with brain metastasis recorded between 2000 and 2017 were included in the study. Brain metastasis was diagnosed radiologically via Magnetic Resonance Imaging or Computerised Tomography (CT). Patient age, sex, radiotherapy dose, number of metastatic masses, distant metastases and surgeries were recorded.

Treatment

All patients were positioned supine in a custom-made mask and received a CT simulation scan of the entire cranium region. All CT scans had 2.5-mm slice thickness. Three-dimensional conformal radiotherapy (3D-CRT) was performed at fractions of 3 Gy daily for a total of 30 to 45 Gy and delivered using 6–18 MV photons. Given the retrospective nature of the study, no randomisation was performed. Clinicians prescribed doses based on the choice of each patient and performance status. The clinical target volume 1 (CTVwb): whole brain, gross target volume 2 (GTVm): metastatic mass or clinical target volume 2 (CTVm): mass bed (MRG is determined by fusion). The planned target volume 1 (PTVwb) was forged with 0.5 cm margins and given up to the CTVwb. The planned target volume 2 (PTVm) was forged with 1.5 cm margins and given up to the GTVm or CTVm. Ten fractions each of 3 Gy for a total of 30 Gy were given up to the PTV1. Five fractions each of 3 Gy for a total of 15 Gy were given up to the PTV2. Therefore, total tumour dose totalled 45 Gy. A daily dose of dexamethasone (4–16 mg) was administered orally during radiotherapy.

Follow-up

After 2 months of RT, all patients were clinically examined. Complete blood test and MRG or CT controls were performed. Overall survival (OS) was described as the time between diagnosis and the last control or death date.

Statistical Analysis

Statistical analysis was performed using the SPSS software (SPSS for Windows, Version 16.0. Chicago, USA). The OS was estimated using the Kaplan–Meier method. The difference in survival rates between the groups was examined using the log-rank test. All results were considered statistically significant at a $p<0.05$.

RESULTS

Of the 296 patients included in the study, 228 (77%) were men and 68 (23%) were women. The median age was 61 years (range: 21–87 years). Overall, 172 (58%) patients were aged 64 years or under, while 124 (42%) were aged 65 years or over. The distribution by number of metastasis in patients was as follows: 61 patients (21%) had solitary brain metastasis, 46 patients (15%) had single brain metastasis, 52 patients (18%) had two-mass brain metastasis (24 patients with only brain metastasis and 28 patients with two-mass brain metastasis plus other metastases) and 137 patients (46%) had multiple brain metastases. In total, 26 patients (8%) were operated for solitary brain metastasis. Patient grouping is addressed in Table 1.

Survival

As of December 2017, the median follow-up period was 7 months (range: 1–57 months). For the entire cohort, the median OS time was 7.81±0.66 months (95% CI: 6.52–9.11) and the 1-year, 2-year and 3-year survival rates were 18.8%, 5.8% and 2.9%, respectively.

The median OS time for patients with solitary brain metastasis who received 30 Gy radiotherapy (Group I) was 10.33± 1.95 months (95% CI: 6.28–13.96). Their 1-year and 2-year survival rates were 41% and 7.8%, respectively. No patient in Group I was alive after 3 years. For patients with solitary brain metastasis who received 45 Gy radiotherapy (Group II), the median OS time was 13.24 ± 2.47 months (95% CI: 8.16–17.83). The 1-year, 2-year and 3-year survival rates for Group II patients were 38.5%, 19.8% and 9.9%, respectively. Although the OS time was higher in the 45 Gy group, the difference was not statistically significant (p=0.504).

The median OS duration of patients with single brain metastasis who received 30 Gy radiotherapy (Group III) was 6.29 ± 0.93 months (95% CI: 4.43–8.09). Their 1-year and 2-year survival rates were 16% and 8%, respectively. No

patient in Group III was alive after 3 years. For patients with single brain metastasis who received 45 Gy radiotherapy (Group IV), the median OS time was 7.40 ± 0.83 months (95% CI: 5.76–9.04). The 1-year, 2-year and 3-year survival rates for Group III patients were 19.1%, 4.8% and 3.6%, respectively. There was no statistically significant difference between the two groups (p=0.301).

In patients with two-mass brain metastasis who received 30 Gy radiotherapy (Group V), median OS time was 9.77 ± 2.10 months (95% CI: 5.64–13.90). Their 1-year and 2-year survival rates were 24.8% and 9.3%, respectively. No patient in Group V was alive after 3 years. In patients with two-mass brain metastasis plus other metastasis (Group VI) who received 30 Gy radiotherapy, median OS time was 6.82 ± 1.19 months (95% CI: 4.49–9.16). The 1-year, 2-year and 3-year survival rates for Group VI were 20.5% and 6.8%, respectively. No patient in Group VI was alive after 3 years.

The median OS duration of patients with multiple brain metastasis who received 30 Gy radiotherapy (Group VII) was 5.52 ± 0.68 months (95% CI: 4.19–6.86). Their 1-year and 2-year survival rates were 8.3% and 4.1%, respectively. No patient in Group VII was alive after 3 years (Table I). A statistically significant difference was noted in the median survival rates among the seven groups (p=0.002) (Table II).

After analysing Group I patients based on surgery and dose of radiotherapy, the median OS time for the WBRT (n=15), surgery + WBRT (n=10), WBRT + conventional boost (n=20) and surgery + WBRT + conventional boost (n=16) cohorts was 9, 12, 14 and 13 months, respectively (p=0.504). The median OS time for patients with solitary brain metastasis who received 30 Gy radiotherapy (Group Ia) was 9.90 ± 2.48 months (95% CI: 5.03–14.76). The 6-month and 12-month survival rates for Group Ia patients were 45.3% and 37.7%, respectively. For patients with solitary brain metastasis who received surgery + 30 Gy radiotherapy (Group Ib), the median OS time was 12.33 ± 3.76 months (95% CI: 4.95–19.71). The 6-month and 12-month survival rates for Group Ib patients were 66.7% and 50%, respectively. There was no statistically significant difference between the two groups (p=0.294).

Table I: Patient Groups

Groups	n (%)	RT Dose	Brain Metastasis	Distant Metastasis
Group I	25 (9)	30 Gy	Single	None
Group II	36 (12)	45 Gy	Single	None
Group III	27 (9)	30 Gy	Single	Present
Group IV	19 (6)	45 Gy	Single	Present
Group V	24 (8)	30 Gy	Two	None
Group VI	28 (10)	30 Gy	Two	Present
Group VII	137 (46)	30 Gy	Multiple	Present

Table II: Survival Analysis in all Patients

Groups	n (%)	RT Dose	Overall Survival (Month) 95% CI	Survival Rate 1 year (%)	Survival Rate 2 year (%)	Survival Rate 3 year (%)	p
Group I	25 (9)	30 Gy	10.33 ± 1.95 6.28-13.96	41.0	7.8	-	0.504
Group II	36 (12)	45 Gy	13.24 ± 2.47 8.16-17.83	38.5	19.8	9.9	
Group III	27 (9)	30 Gy	6.29 ± 0.93 4.43-8.09	16.0	8.0	-	0.301
Group IV	19 (6)	45 Gy	7.40 ± 0.83 5.76-9.04	19.1	4.8	3.6	
Group V	24 (8)	30 Gy	9.77 ± 2.10 5.64-13.90	24.8	9.3	-	0.002
Group VI	28 (10)	30 Gy	6.82 ± 1.19 4.49-9.16	12.0	2.0	-	
Group VII	137 (46)	30 Gy	5.52 ± 0.68 4.19-6.86	8.3	4.1	-	

In patients with solitary brain metastasis who received 45 Gy radiotherapy (Group IIa), the median OS time was 14.70 ± 2.80 months (95% CI: 9.20–20.20). The 6-month and 12-month survival rates for Group IIa patients were 65.4% and 42.6%, respectively. For patients with solitary brain metastasis who received surgery + 45 Gy radiotherapy (Group IIb), the median OS time was 13.86 ± 2.56 months (95% CI: 8.08–18.02). The 6-month and 12-month survival rates for Group IIb patients were 66.2% and 27.2%, respectively. There was no statistically significant difference between the two groups (p= 0.321) (Table III) (Figure 1).

The age-based analysis revealed that the median survival duration for patients under 65 years was 9.65 ± 1.02 months (95% CI: 7.64–11.67), and 5.15 ± 0.51 months (95% CI: 4.15–6.15) for patients of 65 years or over. There was a statistically significant difference in the median survival time between the groups (p<0.001). With regards to surgery, the median survival duration for patients under 65 years was 9.59 ± 1.11 months (95% CI: 7.40–11.78) and 5.03 ± 0.51 months (95% CI: 4.02–6.04) for patients 65 years or over. There was a statistically significant difference in median survival duration between the groups (p<0.001). With regards to surgery, the median survival duration for patients under 65 years was 9.64 ± 1.49 months (95% CI: 6.71–12.57), and 6.74 ± 2.39 months (95% CI: 2.05–11.43) for patients of 65 years or over. There was no statistically significant difference between groups in median survival duration (p=0.387).

Toxicity

During the treatment course, dexamethasone was administered to relieve symptoms. No patient experienced grade 3–4 skin toxicity and no patient died because of surgery or RT.

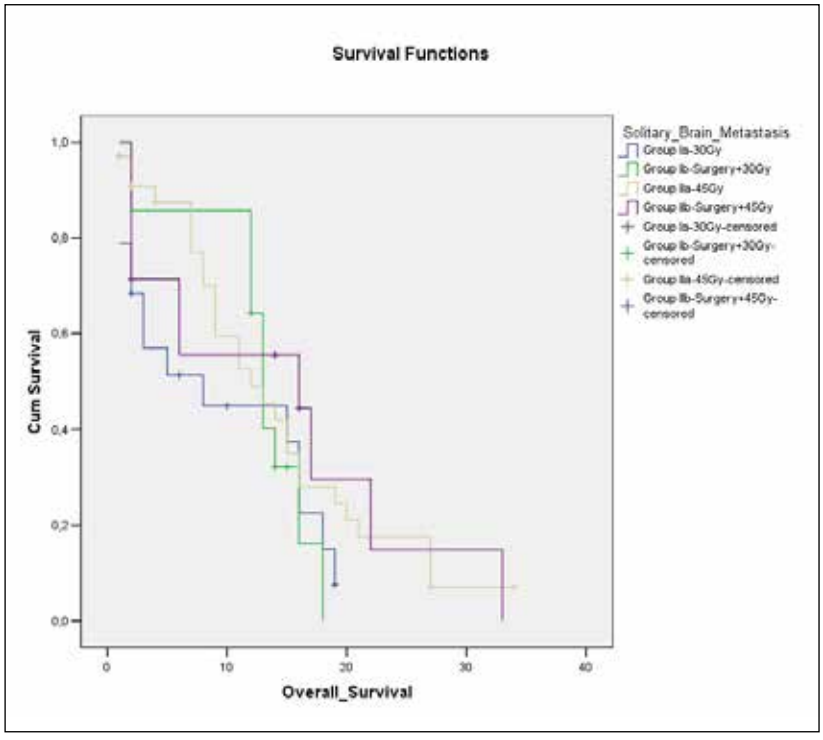

Figure 1: Survival analysis in patients with solitary brain metastasis.

Table III: Survival Analysis in Patients with Solitary Brain Metastasis

		n (%)	OS (Month) (95% CI)	Survival Rate 6 months (%)	Survival Rate 12 months (%)	p	
Group Ia	30Gy	15 (4)	9.90 ± 2.48 5.03-14.76	45.3	37.7	0.294	0.504
Group Ib	Surgery+30Gy	10 (3)	12.33 ± 3.76 4.95-19.71	66.7	50		
Group IIa	45Gy	20 (6)	14.70 ± 2.80 9.20-20.20	65.4	42.6	0.321	
Group IIb	Surgery+45Gy	16 (5)	13.86 ± 2.56 8.08-18.02	66.2	27.2		

DISCUSSION

Brain metastasis is the most common form of intracranial tumour, with high mortality and morbidity rates. It has a high incidence rate in Turkey and the Eastern Black Sea region and it is an important cause of cancer mortality. On average, between 750 and 850 new cancer cases are reported at our clinic every year. Of these cases, between 100 and 150 cases present with brain metastasis. The most common primary causes of brain metastasis reported in our clinic are NSCLC (40–60%), small cell lung cancer (15–20%) and breast cancer (10–15%).

Administration and dosage of WBRT varies from clinic to clinic. The applied dose and fraction ranges from 30 Gy (3 Gy daily) to 40 Gy (2 Gy daily) and to 50 Gy (2 Gy daily) (23). However, no difference in OS was observed among the various dosages and fractions studied (14,26). Consequently, there is no consensus on the optimal radiation dose for patients with brain metastasis (13). In our clinic, 10 fractions each of 3 Gy for a total of 30 Gy were administered for the WBRT and 5 fractions each of 3 Gy for a total 15 Gy were administered to the mass for a total tumour dose of 45 Gy.

The mean survival duration for a patient with untreated brain metastasis is 1–3 months (1). In a study by Harputoglu et al., the median survival duration for NSCLC patients with brain metastasis was 7.2 months and the 1-year survival rate was 20.7% (10). In a study by Sperduto et al., it was shown that the median survival is 7.00 months (range: 6.53–7.50) (24). In a study by Lutterbach et al., it was shown that the median survival is 3.4 months (13). In our study, the median survival was 7.81 ± 0.66 months. In accordance with the literature, the 1-year, 2-year and 3-year OS rates were 18.8%, 5.8% and 2.9%, respectively.

Despite numerous studies designed to improve treatment outcomes, the median survival duration remains between 3 and 6 months (6,18). However, no difference in OS was observed among the various dosages and fraction schemes studied.

A great number of studies indicate that patients with a single brain metastasis have a better chance of survival than those with multiple brain metastases (16,19,24). Nevertheless, some studies show that neither the number of brain metastases nor the intracranial site of brain metastases were significant factors for prognosis (8). The Radiation Therapy Oncology Group study 9508 comparing number of metastases (one to two to three) later provided prospective evidence that the number of brain metastases was prognostic. A survival benefit was confirmed for patients with a single brain metastasis when treated with WBRT plus SRS compared to WBRT alone. However, no survival benefit was seen in patients with two or three brain metastases (2). Comparison among groups showed a statistically significant difference in median survival times. Similar to previous studies, we found that median survival times were better in patients with solitary brain metastasis (p=0.002).

In a prospective study by Ferro et al., IMRT-SIB-WBRT was feasible and safe in a Phase I clinical trial using 30 Gy WBRT with a boost up to 50 Gy (7). The median OS time was 9 months and the 1-year survival rate was 50% for patients treated at doses of 35 Gy and 40 Gy. In patients treated at higher doses, the median OS time was 12 months and the 1-year survival rate was 56.1%. Nichol et al. treated patients who had between 1 and 10 metastases with a similar treatment (volumetric modulated arc therapy (VMRT) SIB), delivering 20 Gy to the whole brain and 47.5 Gy to the metastases in 5 daily fractions. The authors observed a median survival duration of 10.1 months (15). We applied WBRT plus a conventional boost and found a median survival duration of 13.3 months in solitary metastases and 7.4 months in single metastases.

Several retrospective studies administered adjuvant WBRT after resection. Some of these studies suggested a reduction in intracranial relapses and improvements in survival for some patients (4,22). However, in most studies, no improvement in survival was observed (11,21). In a randomised study, the median survival duration was approximately 10 months, with no statistically significant difference between the two groups (17). In a series conducted by Giubilei et al., 30 patients were treated by hypofractionated stereotactic radiotherapy (HSRT) combined with WBRT (30 Gy in 10 fractions). The total doses for HSRT were 18 Gy and 32 Gy. The median survival duration for the overall group of patients after combined treatment was 9.15 months (9). In our study, the median survival duration was 12 months in patients who received surgery + WBRT (n=10) and 13 months in patients who received surgery + WBRT + conventional boost (n=16). These results are comparable to reports from some previous studies. However, there was no statistically significant difference between the groups.

Our study has various limitations. Primarily, it is a retrospective study conducted at a single centre. Therefore, results should be interpreted with caution. In addition, the limited sample size makes it difficult to achieve statistical significance in the subgroup analysis, thereby limiting the power of any conclusions. Also, this retrospective study includes patients treated across a 7-year period. During this period, RT techniques were improved which may have resulted in a selection bias. Furthermore, we only investigated the RT dosage, but comorbidities may also play an important role in patient selection. Finally, we did not analyse the quality of life and neurocognitive impairment.

CONCLUSION

Our patients with solitary and single metastasis tolerated WBRT plus a conventional boost. Although OS rates were numerically better in high dose RT group, the results were not statistically significant. Larger prospective studies are needed to support our findings.

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