Stereotactic Radiosurgery plus Whole-brain Radiotherapy for Treatment of Multiple Metastases from Non-small Cell Lung Cancer

G. MINNITI 1,2, M. SALVATI 2, R. MUNI 1, G. LANZETTA 2, M.F. OSTI 1, E. CLARKE 1, A. COSTA 3, A. BOZZAO 4, G. TRASIMENI 4 and R. MAURIZI ENRICI 1

Departments of 1 Radiotherapy and 4 Neuroradiology, Sant’ Andrea Hospital, University ‘La Sapienza’, Rome, Italy; 2 Department of Neurological Sciences, Neuromed Institute, Pozzilli (IS), Italy; 3 Department of Radiotherapy, Italian Neurological Institute (INI), Grottaferrata, Rome, Italy

Abstract. Background: The aim of this study was to evaluate local control and survival rates after stereotactic radiosurgery (SRS) plus whole-brain radiotherapy (WBRT) for the treatment of multiple brain metastases from non-small cell lung cancer (NSCLC). Patients and Methods: Between June 2004 and September 2008, sixty-six patients with multiple brain metastases from NSCLC were enrolled in this prospective study. All patients were required to have 2-3 brain metastases and Karnofsky performance status (KPS) ≥70. WBRT treatment dose was 30 Gy in 10 fractions followed by SRS. A matched control population treated with WBRT alone to a dose of 30 Gy in 10 fractions was used for comparison. Results: The median survival was 10.3 months in the WBRT plus SRS group and 7.2 months in the WBRT group (p=0.005). The 6-month and 12-month survival rates were 90% and 38% in the SRS plus WBRT group and 84% and 19% in the WBRT group (p=0.01). Stable extracranial disease and KPS were significant predictive factors of survival in both groups (p=0.001). Death due to neurological causes occurred in 18% and 35% of patients treated with WBRT plus SRS and WBRT (p=0.02), respectively. Disease control in the brain was 10 months in the SRS plus WBRT group and 7 months in the WBRT group (p=0.001); the 6-month and 12-month control rates were 82% and 42% for WBRT plus SRS, and 75% and 18% for WBRT (p=0.001), respectively. The 6-month and 12-month control rates of treated lesions (local control) were 90% and 47% in the WBRT group, and 100% and 93% in the WBRT plus SRS group (p=0.001). Conclusion: WBRT plus SRS is a safe, minimally invasive and well-tolerated treatment for patients with up to three brain metastases from NSCLC. The treatment is associated with longer survival and better disease control in comparison with WBRT alone. Survival benefits need to be confirmed by large randomized studies.

Brain metastases develop in up to 40% of patients with non-small cell lung cancer (NSCLC) and represent a terminal stage of the disease (1-3). Most patients with multiple brain metastases are treated with whole-brain radiotherapy (WBRT), with response rates of approximately 40-50% (4-7). The reported median survival in patients with NSCLC treated with WBRT is 3-6 months, with a significant proportion of patients dying of intracranial progressive disease a few months after treatment (1-3, 8-10).

Stereotactic radiosurgery (SRS) has been extensively employed in patients with brain metastasis either alone or in combination with WBRT (11-14). Andrews et al. (13) reported the results from the RTOG 9504 phase III trial on 333 patients with 1 to 3 brain metastasis who received WBRT with or without SRS boost. Survival benefit in the WBRT and SRS group was seen in patients with a single brain metastasis (6.5 months versus 4.9 months, p=0.039). A similar survival advantage with the use of SRS and WBRT as compared to WBRT alone in patients with a single brain metastasis has been reported by several authors (11, 14).

In contrast, the role of SRS in patients with multiple brain metastases is not well defined. Two radiosurgery trials (13, 15) of patients with brain metastases from different primary tumors showed a better 1-year local brain tumor control with WBRT and SRS versus WBRT alone, however this was not associated to an improvement in overall survival. In
some retrospective studies of patients with NSCLC treated with SRS with or without WBRT for 1 to 4 brain metastases, a median survival of 9-14 months has been reported. This finding suggests that aggressive treatment may be associated with survival benefit, especially in patients with no progressive extracranial disease (16-19).

The purpose of this study was to assess the effect of treatment on survival and brain tumor control. The outcome of WBRT plus SRS and of WBRT alone in patients with multiple brain metastases from NSCLC was examined and compared. To reduce the risk of selection bias, this study was performed as a matched-pair analysis.

Patients and Methods

Between June 2004 and September 2008, 66 patients with NSCLC were treated with WBRT plus SRS within a prospective phase II study. Eligible patients were aged 18 years or older, with 2 or 3 brain metastases ≤3 cm on contrast-enhanced magnetic resonance imaging (MRI) scan, derived from a histologically confirmed NSCLC. Patients had a Karnofsky performance status (KPS) score of 70 or higher. Systemic staging radiologic studies were performed immediately before the treatment. Written informed consent was obtained from each patient before entry into the study.

Treatment. The WBRT dosage schedule was 30 Gy in 10 fractions over 2-2½ weeks. The SRS followed WBRT, with a maximum time interval of 3 weeks. All metastatic tumors were treated with LINAC-based SRS. A BrainLab frameless stereotactic system, in conjunction with the BrainScan treatment planning system (Version 5.31) were used for the stereotactic treatment. The target volume was identified on the basis of the fused CT and MRI scans. Metastases with a dimension ≤2 cm were treated with doses of 20 Gy, and metastases of >2 cm with doses of 18 Gy, prescribed to the 80-85% isodose. The gross tumor volume (GTV) was delineated as a contrast-enhancing tumor demonstrated on MRI scans. The planning target volume (PTV) was generated by the geometric expansion of GTV plus 2 mm. Treatment volumes were achieved with 6-10 noncoplanar arcs by using a 6-MV LINAC. Lesions for each patient were treated on 2 or 3 consecutive days in the outpatient clinic.

Follow-up. Patients were examined clinically one month after radiation treatment and then every 2 months. At each visit, neurological status and all complications were recorded according to RTOG CNS toxicity criteria. MRI was performed every 2 months in the first year after the treatment, and then every 3 months or as appropriate according to the clinical indications. The size of treated lesions was measured in three dimensions. Complete and partial response were defined as total radiographic disappearance or decrease in tumor volume >50% of lesion. Local progression was defined as radiographic increase in the size of metastatic lesion. All neuroimaging were reviewed by the same neuroradiologists (G.T. and A.B.) to assess the therapeutic response. For all patients who died, the cause of death (intracranial versus extracranial progression) was determined by clinical/neurological evaluation and brain/systemic radiologic studies.

End points and statistics. The results of the WBRT plus SRS study were compared with a control population treated with WBRT alone to a dose of 30 Gy in 10 fractions, with the use of a matched-pair analysis. Sixty-six patients considered adequate for matching were selected from a database of more than 300 patients treated with WBRT at our Institution or at the Italian Neurological Institute, with the same radiation technique. The groups were matched for age, gender, KPS score, histological tumor type, number of brain metastases (two vs. three), stable primary/extracranial metastatic disease for at least 6 months (no vs. yes), RPA class (RPA 1 vs. RPA 2). Definition of RPA Classes 1 and 2 were: RPA Class 1: KPS ≥70%, age ≤65 years, controlled primary, no extracerebral metastases; RPA Class 2: KPS ≥70%, age ≥65 years and/or uncontrolled primary and/or extracerebral metastases.

The primary end points of the study were to assess overall survival (OS) and brain tumor control. OS, local control (control of irradiated lesions) and brain tumor control were estimated using the Kaplan-Meier method calculated from the time of radiation treatment. The log-rank test was used to compare differences between the Kaplan-Meier curves. Relative risks for treatment found to be significant (p<0.05) were included in a multivariate analysis performed using a Cox proportional hazards regression model.

Results

Between June 2004 and September 2008, 66 eligible patients were treated with WBRT plus SRS. This population was matched to 66 patients treated in our Institution with WBRT alone to a dose of 30 Gy in 10 fractions. The characteristics of the WBRT plus SRS group and WBRT alone group (pair matched group) are listed in Table I. The treatment groups were adequately matched by age, sex, Karnofsky performance status, number of metastases and presence of progressive systemic disease. According to the RTOG recursive partitioning analysis (RPA) classes for brain metastases, 19 patients (29%) were in RPA Class 1, and 47 patients (71%) in RPA Class 2 in each group. Four patients treated with WBRT alone and 6 patients treated with WBRT plus SRS who had intracranial progression had further treatment in form of SRS or surgery at that time. Thirty-eight patients treated with WBRT and 42 patients treated with WBRT plus SRS received chemotherapy during the follow-up. Follow-up data were reported to June 2009. At this time 15 patients in the WBRT plus SRS group and 2 patients in the WBRT group were alive.

Survival and cause of death. Patients who received WBRT alone had a median survival of 7.2 months and patients who received WBRT plus SRS had a median survival of 10.3 months (p=0.0005) (Figure 1). 6-month and 12-month survival rates were 90% (95% CI, 78%-99%) and 38% (95% CI, 24%-52%) in the WBRT plus SRS group, and 84% (95% CI, 70%-98%) and 19% (95% CI, 5%-33%) in the WBRT group (p=0.01).

Univariate and multivariate analysis of survival in each group are shown in Table II. Stable extracranial disease, age, KPS >70, and RPA class were significant predictive factors for survival in both groups. Comparative subgroups analysis...
between patients treated with WBRT plus SRS, and those treated with WBRT alone showed that the presence of stable extracranial disease and RPA class 1 were associated with the most significant survival difference. Median survival was 13.2 months in RPA Class 1 patients treated with WBRT and SRS, and 9.8 months in RPA Class 1 patients treated with WBRT alone (p=0.001). Death was attributed to neurologic causes in 12 patients (18%) in the WBRT plus SRS group and 23 patients (35%) in the WBRT alone group (p=0.02).

**Brain tumor control.** A significant improvement in brain tumor control rate was found after WBRT plus SRS in comparison with WBRT alone. The median time to intracranial tumor progression was 7 months after WBRT alone and 10 months after WBRT plus SRS (p=0.001). The 6-month and 12-month brain tumor control rates were 82% (95% CI, 68%-94.9%) and 42% (95% CI, 27%-57%) in the WBRT plus SRS group, and 75% (95% CI, 61%-89%) and 18% (95% CI, 6%-30%) in the WBRT alone group (p=0.01) (Figure 2). The 6-month and 12-month local control rates were 90% and 47% in WBRT alone group, and 100% and 93% in WBRT plus SRS group (p=0.001) (Figure 3). Tumor in twelve patients in the WBRT group and 4 patients in the WBRT plus SRS group recurred locally. Brain tumor recurrence at distant sites in the brain was similar in the two groups (19 in the WBRT plus SRS group and 21 in the WBRT alone group). In patients treated with WBRT plus SRS, 41 (26%) out of 157 metastases had a complete response, 63 (40%) had a partial response, and 48 (31%) remained stable. Five metastases in 4 patients had increased in size.

Univariate analysis showed that control of extracranial disease and RPA class were significant predictive factors for brain tumor control in both groups (p=0.01). Age, gender, histology, volume and number of metastases did not significantly affect brain tumor control.

**Functional preservation and toxicity.** KPS score rates >70 at 6 and 12 months were 80% and 33% in patients treated with WBRT plus SRS and 70% and 12% in patients treated with WBRT alone (p=0.03). With respect to neurologic status, 35% of patients treated with WBRT plus SRS and 25% of patients treated with WBRT alone experienced either a temporary or permanent clinical improvement in pre-treatment neurologic symptoms. During the follow-up changes in KPS due to neurologic deterioration were observed in 17 (26%) patients treated with WBRT plus SRS and in 30 (45%) patients treated with WBRT alone (p=0.01).

There was no significant acute morbidity related to SRS. In the WBRT plus SRS group, 6 patients developed radionecrosis which was controlled by the use of steroids or surgery in all patients. Six patients who received SRS plus WBRT and five patients who received WBRT alone experienced neurocognitive deficits (grade 2 confusion and/or grade 2 memory loss) without evidence of disease progression within 6-12 months from treatment, and these were recorded as neurotoxic effects of radiation treatment.
Discussion

The diagnosis of multiple brain metastases in patients with NSCLC is frequent and has been associated with a dismal prognosis. WBRT has been the standard treatment for brain metastases for several decades, however progression of brain disease is expected (4-7). More recently, the importance of more aggressive therapies in the form of surgery or SRS with or without WBRT for patients with limited intracranial disease has been increasingly recognized, with a reported survival of 10-14 months (11-14, 17-25).

The present study compared WBRT plus SRS versus WBRT in a series of 132 patients with multiple brain metastases from NSCLC. A significant survival advantage was associated with WBRT plus SRS versus WBRT alone. Patients who received WBRT alone had a median survival of 7.2 months and patients who received WBRT plus SRS had a median survival of 10.3 months (p=0.0005). Analysis of prognostic factors showed that KPS >70 and absence of extracranial disease were the only significant variables in a multivariate analysis. Survival was 13.2 months for RPA class 1 patients treated with WBRT plus SRS and 9.8 months for patients treated with WBRT alone (p=0.001).

The comparison of the two treatment groups was performed as a matched-pair analysis. Despite the adequate match the potential risk of a hidden bias cannot be eliminated and this must be taken into account when interpreting these results. Nevertheless, our study supports SRS as a means of improving survival in patients with multiple metastases from NSCLC. The RTOG 9508 randomized trial (13) failed to find a survival advantage between patients with multiple metastases treated with WBRT plus SRS and WBRT alone, although for patients with NSCLC, survival was longer in the SRS arm compared with the WBRT alone arm (5.9 months vs. 3.9 months, p=0.012).

The significant improvement in brain tumor control found after WBRT plus SRS in comparison with WBRT alone, can explain, at least in part, the better survival rates observed. The 6-month and 12-month brain tumor control rates were 82% and 42% in the WBRT plus SRS group and 75% and 18% in the WBRT alone group, respectively. The 6-month and 12-month control rates of treated lesions were 90% and 47% in WBRT alone group, and 100% and 93% in WBRT plus SRS group (p=0.001). Our observations are in line with previous published data (13, 15). In a small randomized study of 27 patients with 2 to 4 brain metastases, SRS combined with WBRT was shown to be

| Table II. Prognostic factors in WBRT plus SRS and WBRT group. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | WBRT plus SRS   | WBRT plus SRS   | WBRT            |
|                                | Median survival | Univariate      | Multivariate    | Median survival | Univariate      | Multivariate    |
|                                | months          | analysis P-value| analysis P-value| months          | analysis P-value| analysis P-value|
| All patients                   | 10.3            | NS              | 7.2             | 6.5             | NS              | 7.5             |
| Age (years)                    |                 |                 |                 |                 |                 |                 |
| >65                            | 7.3             | 0.002           | 7.5             | 6.7             | NS              | 7.4             |
| ≤65                            | 11.3            | NS              | 11.4            | 7.4             | NS              | 6.9             |
| Gender                         |                 |                 |                 |                 |                 |                 |
| M                              | 9.5             | NS              | 6.7             | 7.4             | NS              | 7.4             |
| F                              | 11.4            | NS              | 7.4             | 6.9             | NS              | 6.9             |
| No. of lesions per patient     |                 |                 |                 |                 |                 |                 |
| 2                              | 10.7            | NS              | 7.4             | 7.4             | NS              | 7.4             |
| 3                              | 9.9             | NS              | 6.9             | 6.9             | NS              | 6.9             |
| Histological type              |                 |                 |                 |                 |                 |                 |
| Adenocarcinoma                 | 10.4            | NS              | 7.3             | 7.3             | NS              | 7.3             |
| Squamous cell carcinoma        | 9.9             | NS              | 7.7             | 7.7             | NS              | 7.7             |
| KPS score                      |                 |                 |                 |                 |                 |                 |
| 70                             | 9.5             | 0.01            | 6.3             | 6.3             | 0.005           | 0.02            |
| 80-100                         | 11.1            | 0.04            | 7.7             | 7.7             | 0.0001          | 0.001           |
| Extracranial disease           |                 |                 |                 |                 |                 |                 |
| Stable                         | 11.4            | 0.0001          | 6.5             | 6.5             | 0.0001          | 0.001           |
| Active                         | 8.0             | 0.01            | 6.5             | 6.5             | 0.0001          | 0.001           |
| RPA class                      |                 |                 |                 |                 |                 |                 |
| 1                              | 13.2            | <0.0001         | 9.8             | 9.8             | <0.0001         | 9.8             |
| 2                              | 9.1             | 0.001           | 6.7             | 6.7             | 0.001           | 6.7             |

WBRT, Whole-brain radiotherapy; SRS, stereotactic radiosurgery.
superior to WBRT alone in the control of brain disease (15). The rate of local failure at 1 year was 100% after WBRT alone, but only 8% in patients who underwent WBRT plus SRS. In the RTOG 9508 trial (13), the tumor control rate at 1 year was better in the WBRT plus SRS group than the WBRT group (p=0.01), and similar results have been reported by others (14, 16).

Brain disease control with WBRT plus SRS was associated with a better preservation of neurological function and decreased risk of neurologic death. Although the assessment of neurologic function was not conducted with sophisticated measures, a worsening of KPS due to neurologic deterioration in patients who had WBRT alone in comparison to those receiving WBRT plus SRS was observed. No other significant toxicity was associated with SRS. With improvements in systemic chemotherapy of NSCLC patients (26-29), aggressive brain treatment with SRS will likely increase in the management of such patients.

Randomized and retrospective studies have compared WBRT plus SRS versus SRS alone in patients with 1 to 4 metastases, suggesting that SRS alone could be a treatment option (13, 15, 22-25). Aoyama et al. (25) in a randomized study of 132 patients have reported that SRS alone without upfront WBRT was associated with increased brain tumor recurrence, however, it did not result in either worsened neurologic function, nor significant survival difference. Similarly, the recent EORTC 22952-26001 study on the adjuvant WBRT versus SRS or surgical resection of 1-3 cerebral metastases showed that adjuvant WBRT reduces the frequency of intracranial progression and neurologic deaths but does not prolong the overall survival time (10.9 months, in both arms; p>0.5) (30). These results suggest that WBRT could be omitted in the initial management of patients with multiple brain metastases. However, SRS alone is associated with increased intracranial progression and a frequent monitoring of brain tumor status is mandatory.

Patients with a limited number of brain lesions may benefit from resection plus WBRT (31-37). In a retrospective analysis of 206 patients with one or two metastases, Rades et al. (36) reported a similar outcome in patients treated with WBRT plus SRS or surgery plus WBRT and boost. The 1-year survival and brain tumor control rates were 65% and 70% after WBRT plus SRS and 63% and 78% after surgery plus WBRT/boost, respectively. A recent small randomized study showed no differences in survival and neurological death rates between patients treated with surgery plus WBRT or SRS alone (35), and similar results have been reported by others (34). Certainly, SRS is less invasive and more cost-effective than resection, and is currently available as a routine outpatient clinic procedure in the majority of radiotherapy departments.

In conclusion, the combination of WBRT and SRS significantly improves survival and intracranial control in patients with multiple brain metastases from NSCLC. The addition of SRS to WBRT was associated with a better preservation of neurologic function and decrease in death due to neurologic causes, with no other significant toxicity. Although the potential survival advantages of an aggressive management of multiple brain metastases from NSCLC need to be confirmed by randomized trials, WBRT plus SRS could be considered as a treatment option for selected patients with 2-3 brain metastases, especially for those with controlled primary disease.
Acknowledgements

We are grateful to Mr Roberto Montagnoli and Miss Francesca Saporetti for their valuable technical assistance during the radiosurgical procedures.

References


