

# Comparative survival in patients with brain metastases from non-small-cell lung cancer treated before and after implementation of radiosurgery

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## ABSTRACT

**Introduction** Survival after a diagnosis of brain metastasis in non-small-cell lung cancer (NSCLC) is generally poor. We previously reported a median survival of approximately 4 months in a cohort of patients treated with whole-brain radiotherapy (WBRT). Since that time, we implemented a program of stereotactic radiosurgery (SRS). In the present study, we examined survival and prognostic factors in a consecutive cohort of patients after the introduction of the SRS program.

**Methods** Data from a retrospective review of 167 NSCLC patients with brain metastasis referred to a tertiary cancer centre during 2010–2012 were compared with data from a prior cohort of 91 patients treated during 2005–2007 (“pre-SRS cohort”).

**Results** Median overall survival from the date of diagnosis of brain metastasis (4.3 months in the SRS cohort vs. 3.9 months in the pre-SRS cohort,  $p = 0.74$ ) was not significantly different in the cohorts. The result was similar when the no-treatment group was excluded from the SRS cohort. Within the SRS cohort only, significant differences in overall survival were observed between treatment groups (SRS, WBRT plus SRS, WBRT, and no treatment), with improved survival being observed on univariate and multivariate analysis for patients receiving SRS compared with patients receiving WBRT alone ( $p < 0.001$ ).

**Conclusions** No improvement in survival was observed for NSCLC patients with brain metastases after the implementation of SRS. Selected patients (younger age, female sex, good performance status, fewer brain metastases) treated with SRS appeared to demonstrate improved survival. However, those observations might also reflect better patient selection for SRS or a greater tendency to offer those patients systemic therapy in addition to SRS.

**Key Words** Non-small-cell lung cancer, brain metastasis, radiosurgery, whole-brain radiotherapy, radio-surgery practice

*Curr Oncol.* 2017 Apr;24(2):e146-e151

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## INTRODUCTION

Brain metastases (bMets) are a common occurrence in patients with advanced lung cancer. Approximately 10% of patients with non-small-cell lung cancer (NSCLC) present with bMets<sup>1</sup>. Estimates suggest that up to 50% of patients will develop bMets during the course of their illness, and that figure appears to be rising<sup>1–4</sup>.

For NSCLC patients with bMets, prognosis is generally poor<sup>5–9</sup>. The goals of treatment are to minimize toxicity and to maximize both length and quality of life<sup>10,11</sup>. Previous evaluation of a cohort of NSCLC patients with bMets at our institution treated primarily with whole-brain radiation therapy (WBRT) with or without surgery demonstrated a median survival of approximately 4 months from diagnosis with bMets<sup>12</sup>.

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Most patients with bMets present with a limited number of lesions (up to 4)<sup>2,3</sup>. The improved toxicity profile associated with newer radiation techniques such as stereotactic radiosurgery (SRS)—in particular, the reduction in late toxicities—has led to a paradigm shift in treatment<sup>4</sup>. The sophisticated planning and imaging techniques in SRS target cranial lesions with high levels of precision<sup>8</sup>, permitting an escalation of the radiation dose to the target lesion or lesions, while sparing the surrounding normal tissues<sup>5–11</sup>. Traditional WBRT has been supplemented with, and more recently replaced by, SRS alone<sup>5–9</sup>. The goal of SRS is tumour ablation, analogous to surgery. However, SRS is minimally invasive and can routinely treat multiple lesions<sup>4</sup>, making SRS an attractive treatment option in the setting of NSCLC with bMets, for which both length and quality of life are the goals of treatment<sup>10</sup>.

The addition of SRS to WBRT was shown, in a planned subgroup analysis in a randomized controlled trial, to improve survival in patients with a single brain metastasis<sup>8</sup>. A subgroup analysis of those data showed an increased survival benefit in patients with NSCLC and bMets<sup>8</sup>. In patients with NSCLC and limited bMets, SRS has become the preferred treatment approach. Recently, a meta-analysis of individual patient data from three randomized controlled trials suggested that SRS alone might confer a survival advantage over SRS plus WBRT in younger patients with 1–4 bMets, despite increased risk after SRS for the development of additional bMets<sup>9</sup>. There is a rationale to consider SRS because of its better side-effect profile compared with that for WBRT<sup>7,10</sup> and its ability to successfully salvage additional bMets<sup>5–7,9</sup>. The sustained control of new central nervous system metastases with the use of salvage SRS might permit more aggressive management of extracranial disease and could potentially increase overall survival (OS) for these patients<sup>11</sup>.

In July 2010, SRS became widely available at our institution. Since that time, we have expanded our use of SRS alone for patients with NSCLC and bMets. Evaluation of that change in policy was an important component of the implementation strategy. We therefore undertook the present study to examine the effect on outcomes in NSCLC patients with bMets after implementation of the SRS program. We hypothesized that the availability of SRS for the treatment of bMets would result in OS improvements for NSCLC patients with bMets in the more recent SRS cohort.

## METHODS

We previously reported management and outcomes for a cohort of NSCLC patients undergoing treatment for bMets during 2005–2007 (“pre-SRS cohort”)<sup>12</sup>. In the present study, we collected treatment and outcomes data for a second cohort of NSCLC patients diagnosed with bMets from July 2010 to December 2012 after implementation of the SRS program (“SRS cohort”).

All patients were treated at the Juravinski Cancer Centre, McMaster University, Hamilton, Ontario, and were followed from the diagnosis of bMets until death. The Juravinski Cancer Centre is a comprehensive cancer centre that provides service to a population of approximately 2 million. Study methods for the pre-SRS cohort were previously described<sup>12</sup>. Patients eligible for the SRS

cohort included those with NSCLC and a diagnosis of bMets, including those treated with supportive care. In contrast, the pre-SRS cohort included only NSCLC patients with bMets who were planned to be treated with brain radiotherapy; it also excluded patients who were referred to other centres for SRS<sup>12,13</sup>. Patients referred from other institutions for SRS were included in the SRS cohort. Patients identified from the electronic medical record were cross-referenced against an internal SRS database to ensure accuracy of the selection process.

All patients were seen in a specialized multidisciplinary bMets clinic. The clinic was attended by a neuro-radiation oncologist and a neurosurgeon. Data extracted from the medical record included demographics, disease information, treatments, and outcomes. Information about date of diagnosis of bMets, number of lesions, treatment of bMets, recurrence of bMets, and any subsequent treatment was also collected. The study was approved by the Hamilton Integrated Research Ethics Board.

The primary outcome was OS in the SRS and pre-SRS cohorts. Secondary outcomes included survival according to the type of radiation used in the SRS cohort and a subset analysis of OS by age group. Summary statistics are used to describe patient characteristics at diagnosis and at presentation with bMets, as well as outcomes. The Fisher exact test, Wilcoxon rank-sum test, and Cochran–Armitage test for trend were used to identify statistically significant differences between the cohorts in patient and tumour characteristics. The Kaplan–Meier method was used to calculate time-to-event outcomes for OS, from the time of bMets diagnosis. Cox proportional hazards regression was used to investigate factors prognostic for the outcomes of interest<sup>14,15</sup>. Forward stepwise selection was used to construct an optimal model of prognosticators. The effect of cohort was tested, adjusting for factors identified in the optimal model. The use of any systemic therapy was summarized. Statistical significance was defined as a *p* value less than 0.05, and all tests were two-sided.

## RESULTS

Table 1 summarizes the characteristics of patients in the pre-SRS (*n* = 91) and SRS (*n* = 167) cohorts. The pre-SRS cohort did not include patients for whom WBRT was not planned. Our primary analysis controlled for that difference by performing two survival analyses: one in which both cohorts were evaluated in total, and the other in which the SRS cohort excluded the no-treatment group. Demographic and baseline disease characteristics were similar between the two cohorts, with the exception of initial NSCLC stage (*p* = 0.004). The patients in the SRS cohort were more likely to be stage IV at initial NSCLC presentation (78.4% vs. 60.4%). In the SRS cohort, 29 patients (17.4%) received no initial cranial radiotherapy for their bMets (therefore receiving supportive care), leaving 138 patients in the SRS cohort in the “intended to have cranial radiotherapy” group.

In comparing the two cohorts, no difference in OS was observed (log-rank *p* = 0.74). The lack of a significant OS difference remained after the no-treatment group was excluded from the SRS cohort. There was similarly no difference in OS between the two cohorts in a multivariate

**TABLE I** Demographic data and treatment summary

| Characteristic                          | Study cohort  |                | <i>p</i> Value     |
|-----------------------------------------|---------------|----------------|--------------------|
|                                         | After SRS use | Before SRS use |                    |
| Patients ( <i>n</i> )                   | 167           | 91             |                    |
| Age at diagnosis (years)                |               |                |                    |
| Mean                                    | 65.7±10.2     | 63.3±10.5      |                    |
| Median                                  | 65.6          | 64.0           |                    |
| Range                                   | 35.7–86.6     | 35.4–83.4      | 0.099              |
| Sex [ <i>n</i> (%) women]               | 85 (50.9)     | 48 (52.8)      | 0.80               |
| Smoking status [ <i>n</i> (%)]          |               |                |                    |
| Nonsmokers                              | 12 (7.2)      | 7 (7.7)        | 0.099              |
| Ex-smokers                              | 80 (47.9)     | 31 (34.1)      |                    |
| Current smokers                         | 75 (44.9)     | 52 (57.1)      |                    |
| Unknown                                 |               | 1 (1.1)        |                    |
| Histology [ <i>n</i> (%)]               |               |                |                    |
| Adenocarcinoma                          | 98 (58.7)     | 47 (51.7)      | 0.54               |
| Small-cell carcinoma                    | 16 (9.6)      | 11 (12.1)      |                    |
| Non-small-cell lung cancer NOS          | 53 (31.7)     | 33 (36.3)      |                    |
| <i>EGFR</i> mutated                     | 11 (6.6)      | NC             |                    |
| <i>ALK</i> mutated                      | 1 (0.6)       | NC             |                    |
| Stage at diagnosis [ <i>n</i> (%)]      |               |                |                    |
| I                                       | 3 (1.8)       | 7 (7.7)        | 0.004 <sup>a</sup> |
| II                                      | 6 (3.6)       | 6 (6.6)        |                    |
| III                                     | 27 (16.2)     | 23 (25.3)      |                    |
| IV                                      | 131 (78.4)    | 55 (60.4)      |                    |
| ECOG performance status [ <i>n</i> (%)] |               |                |                    |
| 0                                       | 30 (18.0)     | 5 (10.2)       | 0.83 <sup>b</sup>  |
| 1                                       | 78 (46.7)     | 28 (57.1)      |                    |
| 2                                       | 30 (18.0)     | 7 (14.3)       |                    |
| 3                                       | 22 (13.2)     | 9 (18.4)       |                    |
| 4                                       | 6 (3.6)       | 0 (0.0)        |                    |
| Unknown                                 | 1 (0.6)       |                |                    |
| Brain metastases [ <i>n</i> (%)]        |               |                |                    |
| Present at diagnosis                    | 71 (42.5)     | 45 (50.0)      | 0.29               |
| Solitary                                | 50 (29.9)     | 34 (37.4)      | 0.27               |
| Multiple                                | 117 (70.1)    | 57 (62.6)      |                    |
| Score on the GPA [ <i>n</i> (%)]        |               |                |                    |
| Median                                  | 1.5           | NC             |                    |
| Range                                   | 0–4           |                |                    |
| Systemic score [ <i>n</i> (%)]          |               |                |                    |
| No evidence of disease                  | 5 (3.0)       | NC             |                    |
| Controlled                              | 22 (13.2)     |                |                    |
| Uncontrolled                            | 24 (14.4)     |                |                    |
| Untreated                               | 115 (68.9)    |                |                    |
| Unknown                                 | 1 (0.6)       |                |                    |
| Neurosurgical procedure [ <i>n</i> (%)] |               |                |                    |
| None                                    | 135 (80.8)    | NC             |                    |
| Brain radiation therapy only            | 1 (0.6)       |                |                    |
| Subtotal resection or greater           | 31 (18.6)     |                |                    |

Initial radiotherapy [*n* (%)]

|              |           |           |
|--------------|-----------|-----------|
| None         | 29 (17.4) | 1 (1.1)   |
| WBRT alone   | 72 (43.1) | 90 (98.9) |
| SRS alone    | 43 (25.8) | 0 (0.0)   |
| SRS and WBRT | 23 (13.8) | 0 (0.0)   |

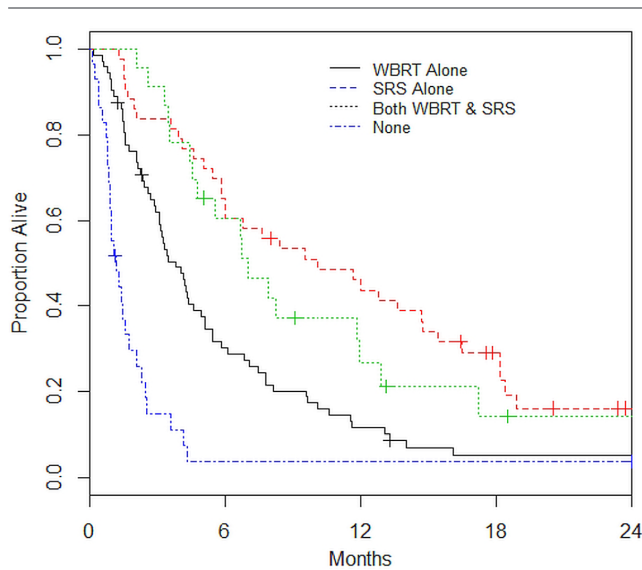
<sup>a</sup> Compared with stage IV.<sup>b</sup> Cochran–Armitage test for trend.

SRS = stereotactic radiosurgery; NOS = not otherwise specified; NC = not collected; ECOG = Eastern Cooperative Oncology Group; GPA = graded prognostic assessment; WBRT = whole-brain radiotherapy.

analysis adjusting for age, Eastern Cooperative Oncology Group performance status, sex, number of bMets, and histology ( $p = 0.88$ , and  $p = 0.39$  after excluding the no-treatment group). For patients in the srs cohort, median os was 1.2 months for supportive care, 3.8 months for WBRT, 10.1 months for SRS alone, and 7.0 months for SRS plus WBRT (Figure 1).

Of the 167 patients in the SRS cohort, 43 had SRS alone as upfront treatment for their bMets, and 23 patients had SRS plus WBRT. Regional brain recurrence was observed in 41.9% of patients receiving SRS alone and in 13.0% of patients receiving SRS and WBRT. “Local recurrence” was defined as a growth in the largest diameter of a treated lesion of more than 20%. Local recurrence was coded only if it was detected less than 12 months after SRS in the setting of positive perfusion magnetic resonance imaging or surgical resection showing viable tumour; otherwise, growth in a treated lesion less than 12 months after SRS was thought to be treatment-related change or radiation necrosis. No local recurrences were observed in the SRS-only group, and local failure was only 8.7% in the SRS plus WBRT group. Salvage WBRT was prescribed in 9 of 43 patients (20.9%) who received upfront SRS alone. Salvage SRS for regional brain progression was performed in 9 of 43 patients (20.9%) in the SRS-only group and in 3 of 23 patients (13.0%) in the SRS plus WBRT group. The median number of salvage SRS treatments was 2 (range: 1–13).

In the SRS cohort, univariable regression analysis showed that age, sex, histology, Eastern Cooperative Oncology Group performance status at diagnosis of bMets, score on the graded prognostic assessment, neurologic symptoms at diagnosis of bMets, pre-diagnosis extracranial radiation therapy, and receipt of initial radiation therapy for the treatment of the bMets were all statistically significant prognostic factors (all  $p \leq 0.004$ , Table II). Multivariable regression analysis on the SRS cohort showed that score on the graded prognostic assessment, neurologic symptoms at diagnosis of bMets, adenocarcinoma histology, female sex, and upfront treatment of the primary disease were all prognostic. Overall survival, adjusted for factors in the optimal model, was significantly worse for patients who were treated with supportive care alone ( $p < 0.001$ ) than for patients treated with WBRT alone (hazard ratio: 0.33; 95% confidence interval: 0.20 to 0.53), SRS alone (hazard ratio: 0.18; 95% confidence interval: 0.10 to 0.31), or both (hazard ratio: 0.20; 95% confidence interval: 0.10 to 0.39). After excluding patients treated with supportive care only, the use of SRS and SRS plus WBRT, compared with WBRT alone,



**FIGURE 1** Survival in the stereotactic radiotherapy cohort by treatment for brain metastases. WBRT = whole-brain radiotherapy; SRS = stereotactic radiosurgery.

were prognostic for longer survival even adjusting for other factors in the optimal model ( $p = 0.001$ ).

Table III presents the uptake of chemotherapy within each cohort according to age group. A clear increase in the uptake of chemotherapy was evident in all age groups in the SRS cohort. Although the interaction between age group and SRS did not attain statistical significance ( $p = 0.094$ ), definite trends were observed. Specifically, in patients less than 60 years of age, a strong trend toward improved survival was evident in the SRS cohort compared with the pre-SRS cohort. However, in patients more than 70 years of age, a trend toward worse survival was observed in the SRS cohort compared with the pre-SRS cohort.

## DISCUSSION AND CONCLUSIONS

Our analysis of two unselected cohorts of patients, one from before and one from after implementation of SRS, observed no change in OS. Although we hypothesized several reasons why the implementation of SRS might improve survival, our findings highlight the complexity in outcomes for patients with NSCLC and bMets<sup>1,14,15</sup>. Given the numerous and complex factors that influence prognosis (for example, burden of systemic disease and performance status), our study highlights the importance of evaluating patient-reported outcomes, quality of life, and the resource implications of new treatment approaches and programs in this population<sup>1,10,14</sup>.

Our study shows that practice has changed significantly over time. In the pre-SRS cohort, WBRT was the only definitive option available locally. In patients with limited prognosis, travel to other centres for SRS would often not be practical, and therefore the best treatment that was locally available was routinely offered to patients. In the SRS cohort, 39.6% of patients received SRS as part of their initial treatment plan. However, many patients with bMets still required WBRT to treat their disease. It is apparent that more

factors than just the presence of bMets are influential in the treatment decisions arrived at by patient and physician. In the SRS cohort, survival outcomes were better for patients who received SRS alone or SRS plus WBRT than for patients treated with WBRT alone (Figure 1, Table II). That finding highlights the potential capability for physicians acting in a specialized bMets clinic, at a tertiary referral cancer centre, to identify NSCLC patients with a more favourable prognosis for the receipt of more individualized bMets treatment<sup>16</sup>.

The choice between SRS alone and SRS plus WBRT in the setting of limited bMets from NSCLC is one with some controversy<sup>5–9</sup>. The addition of WBRT has been associated with lower rates of regional brain recurrence and local control, but also with increased cognitive toxicity<sup>7,10</sup>. In randomized trials, no difference in OS was observed between the two treatment approaches<sup>5–9</sup>. In our SRS cohort, only 20.9% of patients who received upfront SRS alone went on to receive salvage WBRT. That finding supports the use of SRS alone as the preferred upfront management for NSCLC and bMets, given that the focus in this population is providing treatment to maximize disease control and to minimize upfront toxicity, thereby maximizing quality of life<sup>7,10</sup>. The fact that only 20.9% of patients in the SRS cohort who received upfront SRS alone went on to receive salvage WBRT highlights a potential impact of a specialized bMets clinic<sup>16</sup>. Such a clinic would follow a patient closely after initial treatment and would be able to salvage regional brain recurrences with further SRS alone by treating new lesions early and thus preventing the need for WBRT.

At the same time that SRS was introduced for this patient population, other significant changes in management occurred. In patients less than 60 years of age, the uptake of palliative chemotherapy increased, with uptake in the SRS cohort being 75% compared with 34% in the pre-SRS cohort. Those changes also coincided with a trend toward improved survival in patients less than 60 years of age in the SRS cohort compared with their peers in the pre-SRS cohort. That hypothesis-generating outcome is consistent with the recent meta-analysis by Sahgal *et al.*<sup>9</sup>, in which improved survival was observed for patients less than 50 years of age treated with SRS alone compared with those treated with upfront WBRT. One hypothesis that those findings support is that, by limiting the acute toxicity of WBRT, patients and oncologists are more likely to pursue palliative chemotherapy, which could ultimately influence a patient's OS<sup>11,17</sup>.

Our evaluation identified certain subgroups in our SRS cohort for whom survival was improved. Although no overall difference in survival was observed between the two cohorts, patients in the SRS cohort who were treated with upfront SRS or who were less than 60 years of age certainly appeared to have the best outcomes. That observation is consistent with a recent meta-analysis of randomized trials<sup>9</sup>, and we showed that it can be generalized to an unselected NSCLC population with bMets.

One important limitation of our study in the absence of patient-reported quality-of-life data. Although bMets in NSCLC are not routinely curable, the goal of care when managing these patients is to maximize both length and quality of life<sup>7,10</sup>. One of the main reasons that we use SRS to manage bMets is to provide a noninvasive method to control bMets without causing general neurologic toxicity<sup>5–9</sup>.

That approach has opened up many more management options for our patients, as evidenced by an increase in the uptake of systemic therapy and salvage brain radiotherapy, while avoiding WBRT. Without a clear survival benefit across all patients, oncologists must continue to focus on patient selection, determining who is best suited to benefit

from upfront SRS alone and who is best suited for a more supportive treatment regimen<sup>9</sup>. Future prospective studies that evaluate patient-reported quality of life and resource utilization will help to guide oncologists and decision-makers as they continue to develop new methods for the management of the common diagnosis of NSCLC with bMets.

**TABLE II** Regression analysis for overall survival in the stereotactic radiosurgery (SRS) cohort

| Characteristic                            | HR        | 95% CI       | p Value             |
|-------------------------------------------|-----------|--------------|---------------------|
| Univariable model                         |           |              |                     |
| Age at Dx (per decade)                    | 1.35      | 1.15 to 1.58 | <0.001              |
| Female sex                                | 0.58      | 0.41 to 0.80 | 0.001               |
| Smoking status                            |           |              |                     |
| Nonsmoker                                 | 1.32      | 0.69 to 2.50 | 0.48                |
| Ex-smoker                                 | 1.21      | 0.86 to 1.69 |                     |
| Current smoker                            | Reference |              |                     |
| Histology                                 |           |              |                     |
| Adenocarcinoma                            | 0.55      | 0.38 to 0.78 | 0.002               |
| Small-cell carcinoma                      | 1.00      | 0.55 to 1.81 |                     |
| Other                                     | Reference |              |                     |
| Stage at Dx (IV vs. <IV)                  | 0.99      | 0.66 to 1.49 | 0.96                |
| ECOG performance status ≥ 2 <sup>a</sup>  | 2.42      | 1.73 to 3.39 | <0.001              |
| Brain metastasis present at initial Dx    | 0.87      | 0.63 to 1.21 | 0.42                |
| GPA score (per unit)                      | 0.49      | 0.41 to 0.59 | <0.001              |
| Neurologic symptoms present <sup>a</sup>  | 1.68      | 1.18 to 2.39 | 0.004               |
| Treatment before Dx with brain metastasis |           |              |                     |
| Chemoradiation                            | 1.53      | 0.87 to 2.67 | 0.14                |
| Extracranial radiotherapy                 | 2.04      | 1.38 to 3.02 | <0.001              |
| Chemotherapy                              | 1.21      | 0.84 to 1.77 | 0.31                |
| Initial radiotherapy                      |           |              |                     |
| None                                      | Reference |              | <0.001              |
| WBRT alone                                | 0.35      | 0.22 to 0.55 |                     |
| SRS alone                                 | 0.15      | 0.09 to 0.26 |                     |
| SRS and WBRT                              | 0.19      | 0.10 to 0.34 |                     |
| Multivariable model                       |           |              |                     |
| GPA score (per unit)                      | 0.56      | 0.46 to 0.67 | <0.001              |
| Neurologic symptoms present <sup>a</sup>  | 2.36      | 1.52 to 3.67 | <0.001              |
| Histology                                 |           |              |                     |
| Adenocarcinoma                            | 0.46      | 0.32 to 0.68 | <0.001              |
| Small-cell carcinoma                      | 0.59      | 0.30 to 1.14 |                     |
| Other                                     | Reference |              |                     |
| Treatment before Dx with brain metastasis |           |              |                     |
| Extracranial radiotherapy                 | 1.56      | 1.07 to 2.27 | 0.020               |
| Female sex                                | 0.67      | 0.47 to 0.96 | 0.029               |
| Initial radiotherapy                      |           |              |                     |
| None                                      | Reference |              | <0.001 <sup>b</sup> |
| WBRT alone                                | 0.33      | 0.20 to 0.53 |                     |
| SRS alone                                 | 0.18      | 0.10 to 0.31 |                     |
| SRS and WBRT                              | 0.20      | 0.10 to 0.39 |                     |

<sup>a</sup> At diagnosis of brain metastasis.

<sup>b</sup>  $p = 0.010$  if the “no treatment” group is excluded.

HR = hazard ratio; CI = confidence interval; Dx = diagnosis; ECOG = Eastern Cooperative Oncology Group; GPA = graded prognostic assessment; WBRT = whole-brain radiotherapy.

**TABLE III** Chemotherapy use and overall survival in the study cohorts by age

| Age group   | Chemotherapy uptake<br>[n/N (%)] |              | Median survival<br>(months) |              | Survival analysis:<br>with SRS use vs. before SRS use |              |         |
|-------------|----------------------------------|--------------|-----------------------------|--------------|-------------------------------------------------------|--------------|---------|
|             | Before SRS use                   | With SRS use | Before SRS use              | With SRS use | HR                                                    | 95% CI       | p Value |
| <50 Years   | 6/13 (46.2)                      | 12/12 (100)  | 7.5                         | 11.8         | 0.68                                                  | 0.28 to 1.64 | 0.39    |
| 50–59 Years | 4/16 (25.0)                      | 24/36 (66.7) | 3.7                         | 7.8          | 0.48                                                  | 0.23 to 1.01 | 0.05    |
| 60–69 Years | 5/35 (14.3)                      | 32/59 (54.2) | 3.5                         | 4.3          | 0.86                                                  | 0.54 to 1.36 | 0.51    |
| 70–79 Years | 0/21 (0.0)                       | 16/48 (33.3) | 4.3                         | 2.8          | 1.63                                                  | 0.91 to 2.95 | 0.10    |
| ≥80 Years   | 0/4 (0.0)                        | 4/12 (33.3)  | 2.7                         | 1.5          | 1.48                                                  | 0.31 to 7.02 | 0.62    |

Another limitation of this retrospective cohort study is that the populations being compared are likely fundamentally different. We did observe a difference between the populations in stage at presentation; however, other differences that we were not able to observe or measure also likely exist. Those hidden differences make it impossible to understand purely the causes of the results that we observed, thus making our conclusions hypothesis-generating.

Our study found, contrary to our hypothesis, no difference in the primary study outcome. We observed no difference in survival for NSCLC patients with bMets between the pre-SRS and the SRS cohorts. We did observe that, within the SRS cohort, survival was longer in patients who received upfront SRS alone than in those who received upfront WBRT alone. Known patient factors, as shown in our multivariable regression (Table II), remain important for selecting patients for SRS; however, other unknown factors that are influencing outcome are clearly implicitly used by experienced physicians to select patients for SRS. We encourage future research to investigate how best to select NSCLC patients with bMets for the various treatment options. The lack of a major shift in prognosis in our study also highlights the need to focus future research on patient-reported outcomes and quality of life.

#### ACKNOWLEDGMENTS

This work was presented as a mini oral abstract at the International Association for the Study of Lung Cancer 2015 World Conference on Lung Cancer; Denver, CO, U.S.A.; 6–9 September 2015.

#### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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