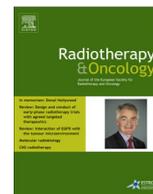


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Brain metastases

Population-based outcomes of boost versus salvage radiosurgery for brain metastases after whole brain radiotherapy [☆]



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ABSTRACT

Purpose: We conducted a retrospective population-based study to examine the survival outcomes in patients with brain metastases treated with salvage stereotactic radiosurgery (SRS), compared to boost SRS, after previous whole brain radiotherapy (WBRT).

Methods and materials: From January 2000 to June 2011, 191 patients treated with WBRT and SRS for brain metastases in British Columbia were studied. Patients were divided into a boost cohort and a salvage cohort. The criteria used to determine eligibility for SRS were: 1–3 metastases, ≤ 4 cm size, Karnofsky performance status ≥ 70 , and control of extracranial disease.

Results: Diagnosis by primary site was 84 lung, 47 breast, 15 melanoma, 12 renal, 9 colorectal, and 24 other. There were 113 patients (59%) in the boost cohort and 78 patients (41%) in the salvage cohort. The median overall survival from WBRT for the whole population was 17.7 months: 12.1 months for the boost cohort and 22.7 months for the salvage cohort. There was no difference in median survival after SRS for the boost and salvage cohorts (11.2 vs. 11.2 months, $p = 0.78$).

Conclusions: In selected patients with brain metastases treated with WBRT, survival following salvage SRS is as good as survival after WBRT + boost SRS.

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The development of brain metastases from a systemic malignancy confers a poor prognosis. Median survival in patients with brain metastases managed with corticosteroids is 2–3 months [1,2]. With whole brain radiotherapy (WBRT) median survival is about 3–6 months [1,3,4]. With the addition of stereotactic radiosurgery (SRS) median survival in selected patients is in the range of 6–12 months [5–8].

The patient outcomes with upfront SRS, as part of the initial management of brain metastases, are well documented in several randomized controlled trials. Most studies report improved local control and median survival of 6–12 months. In a randomized trial by Andrews et al. [5] comparing WBRT with or without SRS boost, mean survival in patients randomized to WBRT + SRS was 6.5 months. In an earlier study by Kondziolka et al. [6] median survival was 11 months for patients with multiple brain metastases treated with WBRT + SRS. Aoyama et al. [7] compared SRS with or without WBRT. Median survival in the SRS + WBRT group was 8.0 months. Other retrospective series using SRS upfront give com-

parable survival outcomes [9–11]. SRS can also be given as salvage treatment at the time of intracranial disease progression after earlier WBRT. The outcomes of salvage SRS are less well known.

With institutional ethics approval, we conducted a retrospective population-based study to examine the survival outcomes in patients with brain metastases treated with salvage SRS, compared to boost SRS, after previous WBRT.

Methods and materials

One hundred and ninety one consecutive patients treated with WBRT and SRS for brain metastases in British Columbia, Canada, from January 2000 to June 2011 were studied. Patients were identified using the institution's stereotactic database, capturing all patients treated with SRS in the province. All patients were reviewed at the provincial stereotactic conference by radiation oncologists, neurosurgeons, and neuro-radiologists. The criteria used by the stereotactic group to determine SRS eligibility were the same as that used by Andrews et al. [5]: 1–3 metastases, ≤ 4 cm size, Karnofsky performance status (KPS) ≥ 70 , and control of extracranial disease. Patients were followed clinically and with computed tomography (CT) or magnetic resonance imaging (MRI) 1–3 months after SRS and then every 3–4 months thereafter. Additional brain imaging was done as neurologic symptoms dictated.

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For SRS planning, patients had a contrast-enhanced CT scan and MRI. Patients were immobilized using a stereotactic halo-type head frame or a frameless stereotactic mask system. CT and MRI scans were co-registered to the BrainLab stereotactic planning software (Brainlab AG, Germany) for treatment planning. The gross tumour volume (GTV) was delineated on the CT/MRI co-registered image data set. A 1 mm (for halo-type head frame) or 1.5 mm (for frameless system) planning target volume (PTV) was constructed using a 3-dimensional volumetric expansion of the GTV. Patients were treated with linear accelerator-based SRS using 3 mm leaf collimation with either multiple static beams or multiple dynamic arcs. Prescription was to the 80% isodose volume covering the PTV. The stereotactic group's dose prescription was the same as described by Shaw et al. [12]: 15 Gy for 31–40 mm size metastases, 18 Gy for 21–30 mm metastases, and 24 Gy for ≤ 20 mm metastases. A dose of 12–15 Gy was used for brainstem metastases.

For analysis, patients were divided into a boost SRS cohort and a salvage SRS cohort. The boost cohort was defined as those patients receiving WBRT with upfront SRS planned as part of initial brain metastases treatment. Patients in this group may have had subsequent repeat WBRT or further SRS as salvage. The salvage cohort was defined as patients receiving SRS at the time of intracranial disease progression, having previously had WBRT. This could be radiographic progression of existing disease or new brain metastases. In the salvage cohort there was no stated intention to deliver SRS upfront. The stereotactic conference report was used to help identify the two cohorts.

Patient survival was calculated using the Kaplan–Meier method. Log-rank analysis was used to compare survival between the two cohorts. Hazards ratios (HR) and confidence intervals (CI) were computed using Cox proportional hazards regression analysis. Univariate analyses were performed to assess the prognostic value of recursive partitioning analysis (RPA) class, presence of extracranial metastases (yes/no), number of brain metastases (1 vs. >1), primary site, and interval from WBRT to SRS on patient survival. The interval from WBRT to SRS was analysed as a continuous variable. Univariate and multivariate analysis was performed on the Kaplan–Meier curves by using the log-rank statistic and the Cox proportional hazards model, with $p < 0.05$ set as the level of significance. No attempt was made to adjust for multiple comparisons.

Results

In the cohort of 191 patients, there were 66 men and 125 women. The median age was 55 years (range, 17–96). Diagnosis by primary site was 84 lung, 47 breast, 15 melanoma, 12 renal, 9 colorectal, and 24 other. At the time of analysis, 27 patients (14%) were alive and 164 (86%) had died. Median clinical follow-up was 15.9 months (range, 0.6–104). Compliance with brain imaging follow-up of surviving patients at 1–3, 4–7, 8–11, and 12–15 months was 82%, 61%, 63%, and 71%, respectively. There were 113 patients (59%) in the boost SRS cohort and 78 patients (41%) in the salvage SRS cohort. Four patients in the boost SRS cohort had subsequent SRS for salvage and five had repeat WBRT for salvage. There was no significant difference in KPS ($p = 0.91$), RPA ($p = 0.27$), or number of brain metastases ($p = 0.94$) between the two cohorts. The median age was younger for the salvage SRS cohort (57 vs. 52 years, $p = 0.004$). The patient characteristics for each cohort are presented in Table 1.

The median WBRT dose and dose per fraction for both cohorts were the same, 30 Gy (range, 20–30 Gy) in 3.0 Gy fractions (range, 2.5–4.0 Gy). A total of 180 brain metastases in the boost SRS cohort and 124 metastases in the salvage SRS cohort were treated. Brain metastasis size was measured using the largest linear dimension in any plane. There was no significant difference in mean metastasis

Table 1

Patient characteristics for boost SRS and salvage SRS cohorts.

		Boost SRS cohort	Salvage SRS cohort
Gender	Male	35 (31%)	31 (40%)
	Female	78 (69%)	47 (60%)
Median age (years)		57	52
Primary site	Lung	56 (50%)	28 (36%)
	Breast	30 (27%)	17 (22%)
	Melanoma	10 (9%)	5 (6%)
	Colorectal	5 (4%)	4 (5%)
	Renal	4 (4%)	8 (10%)
	Other	8 (7%)	16 (21%)
Median KPS		80	80
# of brain metastases	1	65 (58%)	45 (58%)
	2	32 (28%)	22 (28%)
	3	13 (12%)	9 (12%)
	4	3 (3%)	2 (3%)
ECM	Yes	66 (58%)	42 (54%)
	No	47 (42%)	36 (46%)
RPA class	I	34 (30%)	31 (40%)
	II	76 (67%)	47 (60%)
	III	3 (3%)	0 (0%)

Abbreviations: SRS, stereotactic radiosurgery; KPS, Karnofsky performance status; ECM, extracranial metastases; RPA, recursive partitioning analysis.

size between the boost and salvage cohorts, 15.3 vs. 14.4 mm ($p = 0.36$), respectively. The location of brain metastases was also similar between the two cohorts. For both cohorts, the median SRS prescription dose was 24 Gy (range, 12–24 Gy). The tumour and treatment characteristics for each cohort are presented in Table 2.

From the start of WBRT, the median overall survival for the whole population was 17.7 months. The median interval from WBRT to boost SRS was 1.0 months and from WBRT to salvage SRS was 11.0 months. The median overall survival for the boost SRS cohort was 12.1 months and for the salvage SRS cohort was 22.7 months, $p < 0.0001$ (Fig. 1). The 11.0 month interval between WBRT and salvage SRS represents half of the patients' overall survival time for the salvage cohort. There was no difference in median survival between the two cohorts when measured from the date of SRS, 11.2 vs. 11.2 months; $p = 0.78$ (Fig. 2).

On univariate analysis for the boost SRS cohort, the absence of extracranial metastases (HR, 0.63; 95% CI, 0.41–0.96; $p = 0.03$) and RPA I (HR, 0.46; 95% CI, 0.28–0.74; $p = 0.001$) were significant factors for longer survival. A colorectal primary was associated with worse survival (HR, 2.8; 95% CI, 1.1–7.2; $p = 0.03$). In this cohort, the number of brain metastases (1 vs. >1) was not a significant factor. On univariate analysis for the salvage SRS cohort,

Table 2

Tumour and treatment characteristics for boost SRS and salvage SRS cohorts.

		Boost SRS cohort	Salvage SRS cohort
Metastasis size	≤ 20 mm	127 (71%)	92 (74%)
	21–30 mm	44 (24%)	30 (24%)
	31–40 mm	9 (5%)	2 (2%)
Mean size		15.3 mm	14.4 mm
Metastasis location	Supratentorial	145 (81%)	89 (72%)
	Infratentorial	24 (13%)	27 (22%)
	Brainstem	11 (6%)	8 (6%)
SRS dose	12 Gy	3 (2%)	2 (2%)
	15 Gy	21 (12%)	13 (11%)
	18 Gy	51 (28%)	34 (27%)
	24 Gy	105 (58%)	72 (58%)
	Other	0 (0%)	3 (2%)
Mean dose		21.1 Gy	21.1 Gy
Median dose		24 Gy	24 Gy

Abbreviations: SRS, stereotactic radiosurgery.

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