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Abstract

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Stereotactic Radiosurgery and Radiotherapy for Brainstem Metastases: An International Multicenter Analysis

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Abstract

Objectives:

Brainstem metastases (BSM) pose significant neuro-oncological challenges, causing severe neurological deficits and resulting in poor survival rates. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (SRT) may represent viable treatment options despite the delicate location and high single doses. Due to their specific location and poor prognosis, BSM are often excluded from prospective trials, leading to limited data and the absence of larger studies on the use of radiosurgery. This international multicenter study aims to summarize the experience of nine institutions in treating BSM with SRS and SRT.

Methods:

This retrospective international multicenter study included patients treated with SRS or SRT (up to five fractions) for BSM between 2005 and 2022. BSM had to be located in the pons, mesencephalon, or medulla oblongata. Metastases on the brainstem's surface or with presumed invasion from outside were excluded. All patients underwent SRS or SRT using the CyberKnife robotic radiosurgery platform (Accuray Inc., Sunnyvale, CA, USA). The choice of prescription dose, the number of fractions, and applied margin were at the discretion of managing physicians in the nine participating institutions. Patient follow-up was conducted both radiologically and clinically. Local control (LC) was defined as unchanged or decreased tumor volume on follow-up imaging, while local failure (LF) was defined as increased tumor volume during follow-up. In cases of multiple BSM treatments during the disease course, the first treatment was considered for overall survival (OS) and progression-free survival (PFS) calculations. Data analyses utilized the Kaplan-Meier estimator and multivariable Cox proportional hazards models.

Results:

A total of 136 patients with 144 BSM met the inclusion criteria and were analyzed. The median age at treatment was 59.5 years, with the majority suffering from breast cancer (n = 43), non-small cell lung cancer (n = 43), and malignant melanoma (n = 13). The median time from the first cancer diagnosis to BSM SRS or SRT was 28 months. Twenty-five percent of patients received whole brain radiotherapy (WBRT) prior to SRS or SRT. BSM were located in the pons (60%), mesencephalon (29%), and medulla (11%). One hundred patients underwent SRS, with the remainder receiving SRT. The median prescription dose and isodose line for SRS and SRT were 18 Gy and 21 Gy, and 65% and 70%, respectively. The median gross tumor volume (GTV) was 0.42 cc (range 0.01 – 19.7 cc), with larger tumors treated by SRT (median 1.17 cc). In 6% of treatments, a total GTV to planning target volume margin of 1 mm was used, while all other treatments did not apply a margin. The median clinical and radiographic follow-up periods were 9.4 and 6.8 months, respectively. During the available follow-up, 17 LF, 97 progressions (excluding LF and deaths), and 83 deaths were observed. The 1-, 2-, and 3-year LC rates were 82.9%, 71.4%, and 61.2%, respectively. The median time of LC was not reached. The 1-, 2-, and 3-year PFS rates were 21.9%, 4.2%, and 2.1%, respectively, and the 1-, 2-, and 3-year OS rates were 61.1%, 34.7%, and 19.3%, respectively. The median PFS and OS times were 5.5 and 15.7 months. In the multivariable Cox regression analysis for LC, BSM size (in cc, hazard ratio (HR): 1.19), prescription dose (in Gy, HR: 0.78), and SRS (vs. SRT, HR: 0.20) were significantly associated (all p < 0.05). No LF were observed for treatments applying a 1 mm margin. For PFS, only age at the time of BSM

treatment was significantly associated (in years, HR: 0.97, $p = 0.04$). The multivariable analysis for OS revealed good performance status (Karnofsky performance status, $\geq 90\%$; HR: 0.43, $p < 0.01$) and previous WBRT (HR: 2.52, $p < 0.01$) as significant prognostic factors. In five cases, suspicion for the development of radiation necrosis was raised; however, no histopathological information was available for confirmation.

Conclusion(s):

In the absence of comprehensive prospective data, larger studies, and remaining uncertainties concerning normal tissue tolerance of the brainstem, this international multicenter analysis suggests that SRS and SRT for BSM are effective and time-saving treatment options with an acceptable risk profile. Stereotactic treatment with a sufficient dose should be offered to selected patients with small to medium-sized BSM, given the favorable LC rates and overall prognosis.