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## **The Role of CyberKnife Stereotactic Radiosurgery for Renal Cell Carcinoma Brain Metastases**

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Renal Cell Carcinoma (RCC) is a relatively rare systemic cancer which accounts for only about 2% of all cancer cases worldwide, whereas brain metastases from this primary tumor type are reported to occur in approximately 4 to 17% of afflicted patients. Nowadays, stereotactic radiosurgery (SRS) is increasingly used for the treatment of brain metastases with or without prior surgery, and lesions from tumors traditionally considered radioresistant - such as RCC- have shown favorable response rates in numerous studies. The aim of this study was to evaluate the efficacy and potential prognostic factors of SRS for the treatment of brain metastases from RCC on survival, local and distant tumor control at the Beth Israel Deaconess Medical Center (BIDMC, Harvard Medical School, Boston, USA). Therefore, a retrospective analysis of a total of 207 RCC brain metastases encountered in 66 RCC patients in the BIDMC's database who underwent SRS between 2005 and 2013 was performed. A full review of patient records was undertaken with an analysis of respective physics parameters and number and size of brain metastases. SRS was assessed by determining progression free survival (PFS), overall survival (OS), local and distant brain control, side effects and complications. The patient cohort was divided into three treatment subgroups according to their initial treatment modality for brain metastases from RCC: microsurgical resection + SRS, SRS only and whole brain radiation therapy (WBRT) + SRS. Furthermore, potential prognostic factors that correlate with improved survival and local tumor control in these patients were examined. Regarding overall survival, stratifying the patient cohort by their initial treatment modality resulted in a median survival of 13.6 months, 21.9 months and 5.9 months for patients initially treated either with SRS only, with surgical resection + SRS and with WBRT + SRS as their initial treatment. The logrank-test showed statistically significant difference in overall survival comparing the three initial treatment modalities ( $p=0.011$ ). In uni- and multivariate analysis, factors associated with improved overall survival in this study were younger age, prior surgery, lower recursive partitioning analysis (RPA) class, and a good Karnofsky Performance Status (KPS) of  $\geq 70$ . Beyond this, a Score Index for Radiosurgery (SIR)  $\geq 6$ , a higher score in the Basic Score for Brain Metastases (BSBM),  $\leq 3$  brain metastases at initial presentation, and a higher score in the Disease-specific Graded Prognostic Assessment (Ds-GPA) for RCC were also found to be significant prognosticators for good outcome in this analysis. Prior administration of WBRT was associated with poor overall survival. Over the course of the entire follow-up period (mean, 15.8 months; range, 1-84 months), local control was achieved in 193 (93.2%) of 207 treated lesions. In this study, actuarial 1-year local control rates for lesions treated with the three different initial treatment approaches were excellent (SRS only: 84%; surgical resection + SRS: 94%; WBRT + SRS: 88%), but in univariate analysis, no statistically significant differences were found between local control rates of the three subgroups ( $p=0.445$ ), although combined treatment approaches revealed a trend towards better results. The initial tumor volume was found to be the only significant prognostic variable for local PFS in univariate logrank-analysis ( $p<0.0001$ ). During the entire course of follow-up, distant brain failure was observed in 34 (51.5%) patients of the entire cohort. The median time until distant brain failure was 7 months after SRS (95% CI 6-15 months). Median distant brain progression-free survival for patients who initially received SRS alone, surgery + SRS and WBRT + SRS were 19, 7 and 3.5 months,

respectively. In univariate as well as in multivariate analysis, prior WBRT was significantly associated with better distant tumor control ( $p= 0.007$  in univariate analysis and  $p= 0.014$  in multivariate analysis). To date, this retrospective study is the largest study worldwide conducted so far to evaluate the outcome of patients and potential prognostic factors in the treatment of CyberKnife radiosurgery for brain metastases from RCC and the first study comparing the outcomes of these three different treatment subgroups (SRS only, surgery plus SRS, WBRT plus SRS) in this setting at a single institution. Major studies conducted to investigate the effectiveness of SRS for brain metastases from RCC have reported local control rates ranging from 60.9 to 100%. In summary, SRS is a safe and effective treatment option in patients with brain metastases from RCC and results in very favorable local control rates. In case of a patient presenting with a limited number of brain metastases, surgery or SRS might be appropriate, depending on the individual characteristics of the patients and the number, size and location of brain metastasis. Further investigations such as randomized controlled trials are necessary for a more extensive evaluation of prognostic factors and for a comparison of the outcomes of patients treated with SRS alone versus those treated with combined treatment approaches.