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Interactions Between Dose, Cavity Size, and Histology in the Prediction of Local Control Following Stereotactic Radiosurgery for Resected Brain Metastases

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Objectives: In the treatment of resected brain metastases with stereotactic radiosurgery (SRS), recent randomized controlled trials observed local control rates considerably lower than suggested by previous large retrospective studies. To better understand potential methods of improving local control, we constructed quantitative models to evaluate local control as a function of dosimetric and tumor characteristics.

Methods: Patients with brain metastases treated with resection and SRS to the cavity at our institution were evaluated retrospectively. Melanoma, sarcoma, and renal cell carcinoma were considered radio-resistant histologies. Local failure was defined by pathologic confirmation or radiographic progression leading to further overlapping radiation therapy. The dependence of 1-year local control on dose was evaluated with logistic regression. Predictors of local recurrence over time were evaluated with Cox regression. Doses were converted to 3-fraction equivalents, using the linear quadratic model with a/ß = 12 Gy.

Results: Among 150 resection cavities, the most common histologies were lung (40.7%), melanoma (12.7%), renal (12.7%), and breast (11.3%). Forty-one cavities (27.3%) were radio-resistant by histology. Resection was subtotal in 11 cases (7.3%) and gross total in the remainder. The median prescription was 21 Gy (range 15-25) delivered in 3 fractions (range 1-5). The median prescription isodose line was 68% (range 50-74). Median CTV and PTV volumes were 9.1 mL (range 0.7-50.2) and 14.6 mL (range 1.3-65.4), respectively. Five cases (3.3%) of biopsy-proven radionecrosis were observed. Local recurrence occurred in 20 cases (13.3%), at median 6.3 months (range 0.7-43.1) after SRS. Larger cavities were associated with poorer local control. Stratifying by a threshold PTV volume of 12 mL, 63 (42%) and 87 (58%) cavities were categorized as small and large, respectively. When controlling for D95 and gross versus subtotal resection, Cox regression demonstrated significantly greater risk of local failure among large cavities (HR=4.1, 95% CI=[1.4-11.9], p=0.01). Logistic regression identified relationships between maximum dose (Dmax) and local control among small and large radio-resistant

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cavities. For small radio-resistant cavities, Dmax of 30, 35, and 40 Gy were associated with 86%, 95%, and 98% 1-year local control. For large radio-resistant cavities, Dmax of 30, 35, and 40 Gy were associated with 69%, 79%, and 86% 1-year local control, consistent with overall higher rates of recurrence among large cavities. Among large radio-resistant cavities, similar dose-response relationships were appreciated with D50 instead of Dmax, but not with D90, D95, D99, or Dmin. Furthermore, Cox regression demonstrated that greater Dmax was significantly associated with lower risk of local recurrence among large radio-resistant cavities, when controlling for D99 (HR=0.34/Gy, 95% CI=[0.12/Gy,0.96/Gy], p=0.04).

Conclusions: In the treatment of resected brain metastases with SRS, local control among small and large cavities of radio-resistant histology may be improved with greater maximum dose. Understanding the risks of toxicity established by previous studies, cautious investigation of dose escalation based on cavity size and histology may be warranted.