

## Scientific Article

# A Dose-Response Model of Local Tumor Control Probability After Stereotactic Radiosurgery for Brain Metastases Resection Cavities



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## Abstract

**Purpose:** Recent randomized controlled trials evaluating stereotactic surgery (SRS) for resected brain metastases question the high rates of local control previously reported in retrospective studies. Tumor control probability (TCP) models were developed to quantify the relationship between radiation dose and local control after SRS for resected brain metastases.

**Methods and Materials:** Patients with resected brain metastases treated with SRS were evaluated retrospectively. Melanoma, sarcoma, and renal cell carcinoma were considered radio-resistant histologies. The planning target volume (PTV) was the region of enhancement on T1 post-gadolinium magnetic resonance imaging plus a 2-mm uniform margin. The primary outcome was local recurrence, defined as tumor progression within the resection cavity. Cox regression evaluated predictors of local recurrence. Dose-volume histograms for the PTV were obtained from treatment plans and converted to 3-fraction equivalent doses ( $\alpha/\beta = 12$  Gy). TCP models evaluated local control at 1-year follow-up as a logistic function of dose-volume histogram data.

**Results:** Among 150 cavities, 41 (27.3%) were radio-resistant. The median PTV volume was 14.6 mL (range, 1.3-65.3). The median prescription was 21 Gy (range, 15-25) in 3 fractions (range, 1-5). Local control rates at 12 and 24 months were 86% and 82%. On Cox regression, larger cavities (PTV > 12 cm<sup>3</sup>) predicted increased risk of local recurrence ( $P = .03$ ). TCP modeling demonstrated relationships between improved 1-year local control and higher radiation doses delivered to radio-resistant cavities. Maximum PTV doses of 30, 35, and 40 Gy predicted 78%, 89%, and 94% local control among all radio-resistant cavities, versus 69%, 79%, and 86% among larger radio-resistant cavities.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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**Conclusions:** After SRS for resected brain metastases, larger cavities are at greater risk of local recurrence. TCP models suggests that higher radiation doses may improve local control among cavities of radio-resistant histology. Given maximum tolerated doses established for single-fraction SRS, fractionated regimens may be required to optimize local control in large radio-resistant cavities. © 2020 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

In the treatment of brain metastases after surgical resection, one of the primary motivations for choosing stereotactic radiosurgery (SRS) over whole brain radiation therapy (WBRT) is better preservation of neurocognitive function.<sup>1,2</sup> Furthermore, many large retrospective studies have shown excellent rates of local control following SRS for resection cavities, often exceeding 80% at 1 year after treatment.<sup>3-30</sup>

In contrast, 2 randomized controlled trials recently described higher rates of local recurrence within the resection cavity than previously reported in retrospective studies,<sup>1,2</sup> suggesting that SRS may provide inferior local control compared with WBRT.<sup>1</sup> One possible explanation is that these findings reflect a need for improved target delineation. For example, larger uniform expansions of the target volume<sup>31</sup> or application of advanced imaging modalities to better identify residual active tumors<sup>32</sup> may be needed to improve local control. However, an alternative hypothesis is that the rates of local control in these trials reflect lower prescription doses compared with current standards. In the randomized controlled trial conducted by Mahajan et al,<sup>2</sup> patients received a median dose of 16 Gy in 1 fraction (range, 12-18), compared with higher median doses in several recent retrospective studies that treated with a single fraction.<sup>3-5</sup> Potential reasons for poorer control rates in the postoperative setting compared with intact brain metastases include greater tumor hypoxia, disruption of the tumor microenvironment, and microscopic contamination related to surgical intervention. Quantitative modeling may help to predict the effect of higher radiation doses in improving local control.

To better understand the causes of local treatment failure after SRS for resected brain metastases, this study sought to (1) investigate patient, disease, and treatment characteristics as predictors of local recurrence and (2) develop tumor control probability (TCP) models that estimate 1-year local control as a function of radiation dose to the target volume. These data demonstrate that higher doses were associated with substantially greater rates of local control among resection cavities of radio-resistant histology but not among cavities of radio-sensitive histology. Given established maximum tolerated doses (MTDs) for single-fraction treatments,<sup>33</sup> these data suggest that, although single-fraction SRS may provide

excellent local control for small targets, fractionated regimens may be required to optimize local control in patients with large radio-resistant cavities.

## Methods and Materials

### Patient, tumor, and treatment characteristics

Patients with brain metastases from solid tumors treated with surgical resection followed by frameless robotic SRS to the resection cavity at a single institution between 2011 and 2016 were eligible for inclusion if they received follow-up magnetic resonance imaging (MRI) after completion of SRS. Before data collection, institutional review board approval was obtained. Patient consent was not required to conduct this retrospective study owing to minimal risk and because a significant proportion of eligible patients were likely to be deceased at the time of data collection.

Patient, disease, and treatment characteristics were collected retrospectively. Age was defined at the time of surgical resection. Tumor histology was identified based on the surgical specimen from resection of the brain metastasis. Melanoma, sarcoma, and renal cell carcinoma were considered radio-resistant subtypes, based on a prior analysis of 83 radio-resistant brain metastases.<sup>34</sup> The extent of surgical resection (gross total vs subtotal) was determined by an independent radiologist's evaluation of the postoperative MRI, typically obtained within 24 hours of surgery. Concurrent timing of systemic therapy was defined as on the same day as SRS, in cases of daily regimens, or at least 1 cycle before SRS and at least 1 cycle after, in cases of cyclic regimens. Chemotherapy was defined as treatment with cytotoxic agents or tyrosine kinase inhibitors. Immunotherapy was defined as treatment with anti-programmed cell death protein 1 or anti-programmed death-ligand 1 agents.

### SRS and dose-volume histogram analyses

All patients received SRS to the brain metastasis resection cavity in 1 to 5 consecutive daily fractions. The clinical target volume (CTV) was defined as the region of abnormality on T1 post-gadolinium MRI. The planning target volume (PTV) was typically defined per our institutional practice as a 2-mm uniform expansion of the CTV. Because the study period predates the recently

published consensus contouring criteria for resected brain metastases,<sup>35</sup> there was no standard institutional policy regarding contouring of the surgical tract or overlying meninges.

Data obtained from SRS treatment plans included the prescribed dose and fractionation, dose-volume histogram (DVH) data, PTV volumes, percent coverage of the PTV by the prescription dose, and conformity of the dose distribution with respect to the PTV. DVH data included doses delivered to 99%, 95%, 90%, 50%, and 0.03 cm<sup>3</sup> of the PTV (D99%, D95%, D90%, D50%, D0.03 cm<sup>3</sup>), and the maximum dose delivered to the PTV (D<sub>max</sub>). Dose conformity with respect to the PTV was evaluated by the conformity index (prescription volume/target volume) and the new conformity index.<sup>36,37</sup>

### Local tumor recurrence and imaging follow-up

The primary outcome was local tumor recurrence in the resection cavity, defined as fulfillment of either of 2 criteria: (1) a lesion on T1 post-gadolinium MRI overlapping the original resection cavity that was surgically resected and pathologically confirmed to be a recurrence of the original brain metastasis, or (2) a lesion on T1 post-gadolinium MRI overlapping the original resection cavity that was not resected but was judged by the patient's oncology team based on serial MRI to be highly suspicious for recurrence, resulting in a recommendation of a second course of radiation therapy. This second course of radiation therapy could consist of either a second course of SRS or WBRT in cases of diffuse metastatic disease in addition to likely local recurrence. Follow-up MR imaging was obtained according to our institutional practice at approximately every 3 months during the first year after SRS, every 4 months during the second year, and every 6 months thereafter. Outcomes of surgical pathology were obtained from retrospective review. Specimens containing any amount of residual active tumor were considered as evidence of local treatment failure.

### Statistical analyses

Time to local recurrence was assessed using Kaplan-Meier models, censoring at the time of last brain MRI. Univariate Cox regression was performed to assess patient, disease, and treatment characteristics as individual predictors of local recurrence. For survival analyses, tumor location was dichotomized as supratentorial versus infratentorial, and histology was dichotomized as radio-resistant versus radio-sensitive. DVH data were not included as predictors in Cox regression, as they were considered to be better evaluated within TCP models.

Multivariate Cox regression was performed to assess independent predictors of local recurrence. An initial model included all patient, disease, and treatment

characteristics at least weakly associated with local recurrence on univariate Cox regression ( $P < .07$ ). A final parsimonious model was produced by eliminating covariates that did not improve the overall model quality, as assessed by the Akaike Information Criterion. Statistical significance was defined as  $P < .05$ . Survival analyses were performed in R version 3.4.4.<sup>38</sup>

TCP models were developed to estimate the probability of local tumor control at 1 year after SRS as a function of DVH data for the PTV. Thus, only patients who experienced local recurrence within 1 year of SRS and patients with MR imaging of the brain after minimum 1-year follow-up were analyzed in these models. As most patients received SRS in 3 fractions, DVH data for the PTV were converted to biologically equivalent doses in 3 fractions (3fxED). An  $\alpha/\beta$  of 12 Gy was used, based on one of the largest meta-analyses of SRS for brain metastases published to date, which includes a quantitative dose-response analysis.<sup>39</sup> The DVH evaluator tool<sup>40</sup> was used to estimate the relationships between 1-year local tumor control probability and dose (3fxED) to various proportions of the PTV (D99%, D95%, D90%, D50%, D0.03 cm<sup>3</sup>, D<sub>max</sub>) as logistic functions. Logistic dose-response relationships were estimated in this way for the overall cohort and subgroups.

## Results

### Patient, disease, and treatment characteristics

During the study period, 150 brain metastases in 134 patients were treated with surgical resection and SRS to the resection cavity at our institution and received follow-up MR imaging. Patient and disease characteristics are given in Table 1. The most common histologies were lung (40.7%), melanoma (12.7%), renal (12.7%), and breast (11.3%). Forty-one resected tumors (27.3%) were of radio-resistant histology.

Treatment characteristics are given in Table 2. Surgical resection was subtotal in 11 cases (7.3%) and gross total in the remainder (92.7%). Forty-two patients (28%) received chemotherapy or immunotherapy concurrently with SRS. The median prescription was 21 Gy (range, 15-25) in 3 fractions (range, 1-5). Most patients (66.7%) received radiation in 3 fractions. The median prescription isodose line was 68% (range, 50-79). The median PTV volume was 14.6 mL (range, 1.3-65.4). When stratifying by a PTV volume of 12 cm<sup>3</sup>, 87 cavities (58%) were considered large and 63 cavities (42%) were considered small.

### Local tumor recurrence

Sixteen resection cavities (10.7%) were treated with a second surgical resection for progressive enhancement on follow-up T1 post-gadolinium MRI. Upon review of

**Table 1** Patient and disease characteristics

	Number (%) or median (range)
Age (years)	61.4 (23.8-89.6)
Sex	
Female	85 (56.7%)
Tumor location	
Frontal	45 (30%)
Parietal	40 (26.7%)
Temporal	24 (16%)
Occipital	19 (12.7%)
Cerebellar	22 (14.7%)
Histology	
Lung	61 (40.7%)
Renal	19 (12.7%)
Melanoma	19 (12.7%)
Breast	17 (11.3%)
Head and neck	6 (4%)
Endometrial	4 (2.7%)
Ovarian	4 (2.7%)
Colon	3 (2%)
Sarcoma	3 (2%)
Other	14 (9.3%)
Radio-resistant	41 (27.3%)
Uncontrolled	83 (55.3%)
primary disease	
at the time of brain	
metastasis treatment	
Extracranial metastases	39 (26.0%)
present at the time of	
brain metastasis	
treatment	

surgical specimens, 5 cases (3.3%) demonstrated radionecrosis and 11 cases (7.3%) demonstrated active tumor consistent with local tumor recurrence. In addition, 9 cases (6.0%) demonstrated radiographic local recurrence on follow-up MRI that preceded a decision to treat with a second course of radiation therapy, but not a second resection. Thus, 20 total cases (13.3%) of local tumor recurrence were evaluated in this study. Actuarial rates of local control at 6, 12, and 24 months after SRS were 92% (95% confidence interval [CI] = 88%-97%), 86% (95% CI = 79%-93%), and 82% (95% CI = 74%-90%), respectively (Fig 1). Among cases in which local recurrence was not observed, the median time between SRS and the latest brain MRI was 12.1 months.

**Greater resection cavity volume is associated with increased risk of local recurrence**

On univariate Cox regression (Table 3), large cavities (PTV > 12 cm<sup>3</sup>) were significantly associated with local recurrence (hazard ratio, 3.1; 95% CI = 1.1, 8.6; P = .03). Among large cavities, actuarial rates of local control at 6, 12, and 24 months after SRS were 94% (95% CI =

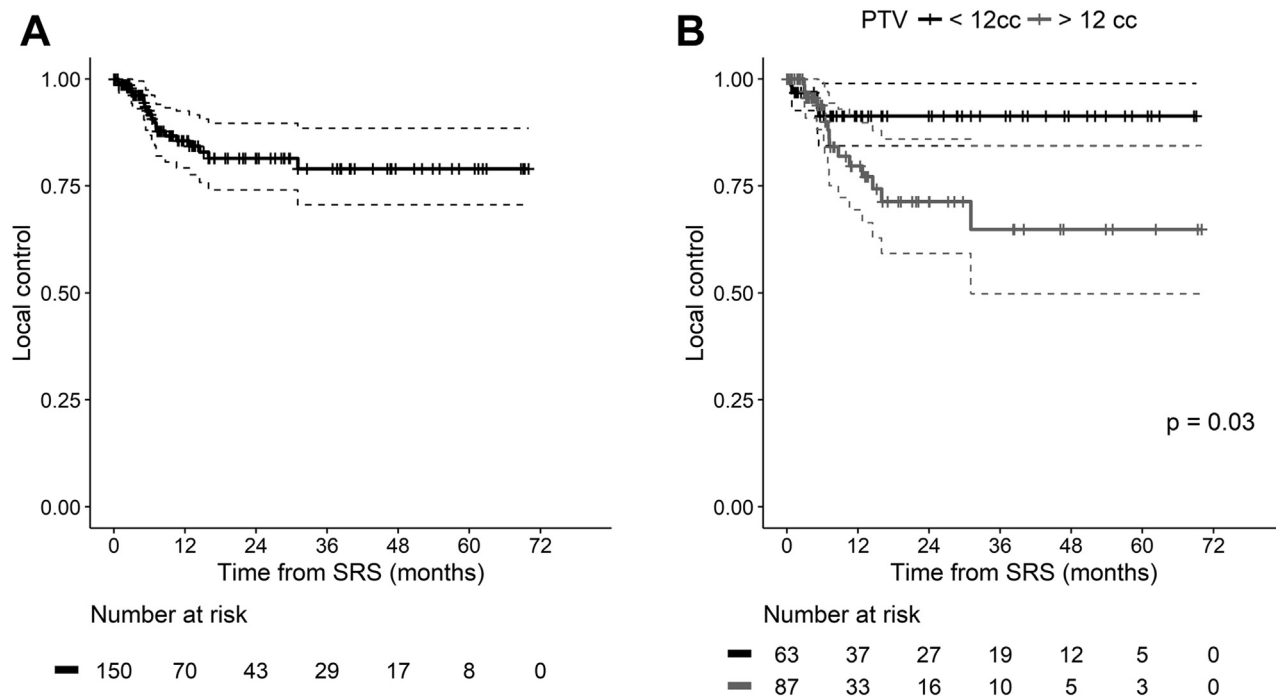
**Table 2** Treatment characteristics

	Number (%) or median (range)
Resection	
Subtotal	11 (7.3%)
Gross total	139 (92.7%)
Prior radiation to same lesion (before resection)	4 (2.7%)
Time from resection to postoperative SRS, mo	1.22 (0.69-5.91)
Parallel systemic treatment	
Chemotherapy	33 (22.0%)
Immunotherapy	9 (6.0%)
Prescription	
Total dose, Gy	21 (15-25)
Dose per fraction, Gy	7 (4-20)
Fractions	3 (1-5)
Isodose, %	68 (50-79)
PTV volume, cm <sup>3</sup>	14.6 (1.27-65.4)
PTV volume >12 cm <sup>3</sup>	87 (58.0%)
Three-fraction equivalent dose (3fxED) to the PTV, Gy	
D99%	21.8 (15.5-29.1)
D95%	22.7 (18.1-29.9)
D90%	23.2 (18.6-30.8)
D50%	26.3 (20-36.1)
D0.03 cm <sup>3</sup>	31.9 (23.6-50)
D <sub>max</sub>	32.5 (24.3-51.7)
PTV coverage, %	97.7 (58.7-100)
Conformity index	1.24 (1.04-20.1)
NCI	1.27 (1.07-20.3)
Number of intact brain metastases treated concurrently	1 (0-10)

Abbreviations: NCI = new conformity index; PTV = planning target volume; SRS = stereotactic surgery.

88%-100%), 80% (95% CI = 69%-91%), and 71% (95% CI = 59%-86%) (Fig 1). Among small cavities (PTV < 12 cm<sup>3</sup>), the actuarial rate of local control at 6 months was 91% (95% CI = 88%-100%), and no further cases of local recurrence were observed after 6-month follow-up (Fig 1). Large cavities were more likely to be of breast histology, were less likely to be of lung histology, and received slightly lower doses (median 3fxED D95% 22.3 Gy vs 24.2 Gy among small cavities) (P < .05). Other than PTV volume, no patient, disease, or treatment characteristics were significantly correlated with local recurrence on univariate Cox regression.

On multivariate Cox regression (Table 3), large cavities (PTV > 12 cm<sup>3</sup>) remained significantly associated with local recurrence (hazard ratio, 3.3; 95% CI = 1.1-9.8; P = .03). Concurrent systemic therapy was associated with lower risk of local recurrence, and subtotal resection was associated with greater risk of local recurrence, but these correlations did not reach the threshold of



**Figure 1** Local tumor control over time. Kaplan-Meier functions for the overall cohort (A) and resection cavities stratified by planned target volume (PTV) greater than or less than 12 cm<sup>3</sup> (B) are shown. Dotted lines represent 95% confidence intervals. The *P* value (B) represents the outcome of univariate Cox regression.

statistical significance ( $P = .10$ ,  $P = .08$ , respectively) (Table 3).

### Higher radiation doses are associated with improved local control among radio-resistant cavities

Logistic regression was performed to assess relationships between DVH data (3fxED) and local tumor recurrence at 1 year after SRS. No meaningful dose-response was observed with respect to any proportion of the PTV (D99%, D95%, D90%, D50%, D0.03 cm<sup>3</sup>, D<sub>max</sub>) when evaluating the overall cohort or the subgroup of patients with radio-sensitive cavities (Fig 2 and Fig E1). However, a meaningful dose-response relationship was observed with respect to all proportions of the PTV (D99%, D95%, D90%, D50%, D0.03 cm<sup>3</sup>, D<sub>max</sub>) among patients with radio-resistant cavities (Fig 2 and Fig E2).

Further stratifying by the threshold PTV of 12 cc revealed dose-response relationships among large radio-resistant cavities, with respect to D50%, D0.03 cm<sup>3</sup>, and D<sub>max</sub>, but not D90%, D95%, or D99% (Fig 3 and Fig E3). Furthermore, large radio-resistant cavities demonstrated lower estimated rates of local control at the same doses compared with all radio-resistant cavities, which reiterates the importance of tumor volume observed on survival analysis. Among all radio-resistant cavities, D<sub>max</sub> of 30, 35, and 40 Gy were associated with 78%, 89%, and 94% 1-year local control (Fig 2), whereas among large radio-

resistant cavities, D<sub>max</sub> of 30, 35, and 40 Gy were associated with 69%, 79%, and 86% 1-year local control (Fig 3).

### Discussion

In the treatment of brain metastases, retrospective studies suggest that resection followed by SRS to the cavity provides excellent local control, often exceeding 80% at 1-year follow-up.<sup>3-30</sup> However, recent randomized controlled trials report considerably lower rates of 1-year local control, ranging from 61.8% to 72%.<sup>1,2</sup> These findings demand a more sophisticated understanding of the factors that influence local treatment failure after resection cavity SRS. As such, we present detailed dose-response models of local tumor control probability based on one of the largest single-institution series of post-operative SRS for resected brain metastases.

Our data are consistent with prior studies reporting higher rates of local recurrence in patients with larger preoperative tumors<sup>2,4,6-9</sup> or larger postoperative resection cavities.<sup>4,9-15</sup> Specifically, PTV volumes greater than 12 cm<sup>3</sup> to 17 cm<sup>3</sup> and CTV volumes greater than 8 cm<sup>3</sup> to 10 cm<sup>3</sup> have been shown to predict greater risk of local recurrence.<sup>9-13</sup> Similarly, we report a 3 times higher risk of local recurrence among cavities with PTV greater than 12 cm<sup>3</sup>. Consequently, larger resection cavities may

**Table 3** Results of univariate Cox regression and final multivariate Cox model assessing predictors of local recurrence

Variable	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age, y	0.99	0.95-1.03	.64			
Female sex	1.24	0.49-3.11	.65			
Infratentorial location	1.10	0.32-3.76	.88			
Radio-resistant	0.56	0.19-1.68	.30			
Prior radiation to same lesion	2.13	0.28-16.0	.46			
Parallel chemotherapy	0.49	0.14-1.67	.25			
Parallel immunotherapy	0.65	0.09-4.86	.67			
Parallel chemotherapy or immunotherapy	0.48	0.16-1.45	.19	0.33	0.09-1.22	.10
Time from surgery to SRS, mo	0.98	0.58-1.65	.94			
Subtotal resection	1.73	0.40-7.50	.46	4.03	0.84-19.3	.08
PTV volume, cm <sup>3</sup>	1.02	0.99-1.05	.18			
PTV volume >12 cm <sup>3</sup>	3.10	1.12-8.57	<b>.03</b>	3.28	1.09-9.83	<b>.03</b>
PTV coverage, %	0.99	0.93-1.05	.67			
Conformity index	0.96	0.76-1.21	.72	0.97	0.91-1.05	.49
NCI	0.97	0.79-1.20	.80			
Number of intact brain metastases treated concurrently	0.95	0.74-1.21	.68			

Abbreviations: CI = confidence interval; HR = hazard ratio; NCI = new conformity index; PTV = planning target volume; SRS = stereotactic surgery.

All variables with  $P < .7$  on univariate analysis were included in the initial multivariate model. Variables that did not improve the Akaike Information Criterion were excluded from the final multivariate model.

Bold indicates statistical significance at  $P < .05$ .

require specific strategies for improving local control beyond the current standard of care.

The primary purpose of this study was to use quantitative models to describe the relationship between radiation dose and local tumor control. TCP modeling suggested that higher doses were associated with substantially greater rates of local control among resection cavities of radio-resistant histology, and particularly among large radio-resistant cavities. However, higher doses were not associated with substantially greater rates of local control among cavities of radio-sensitive histology.

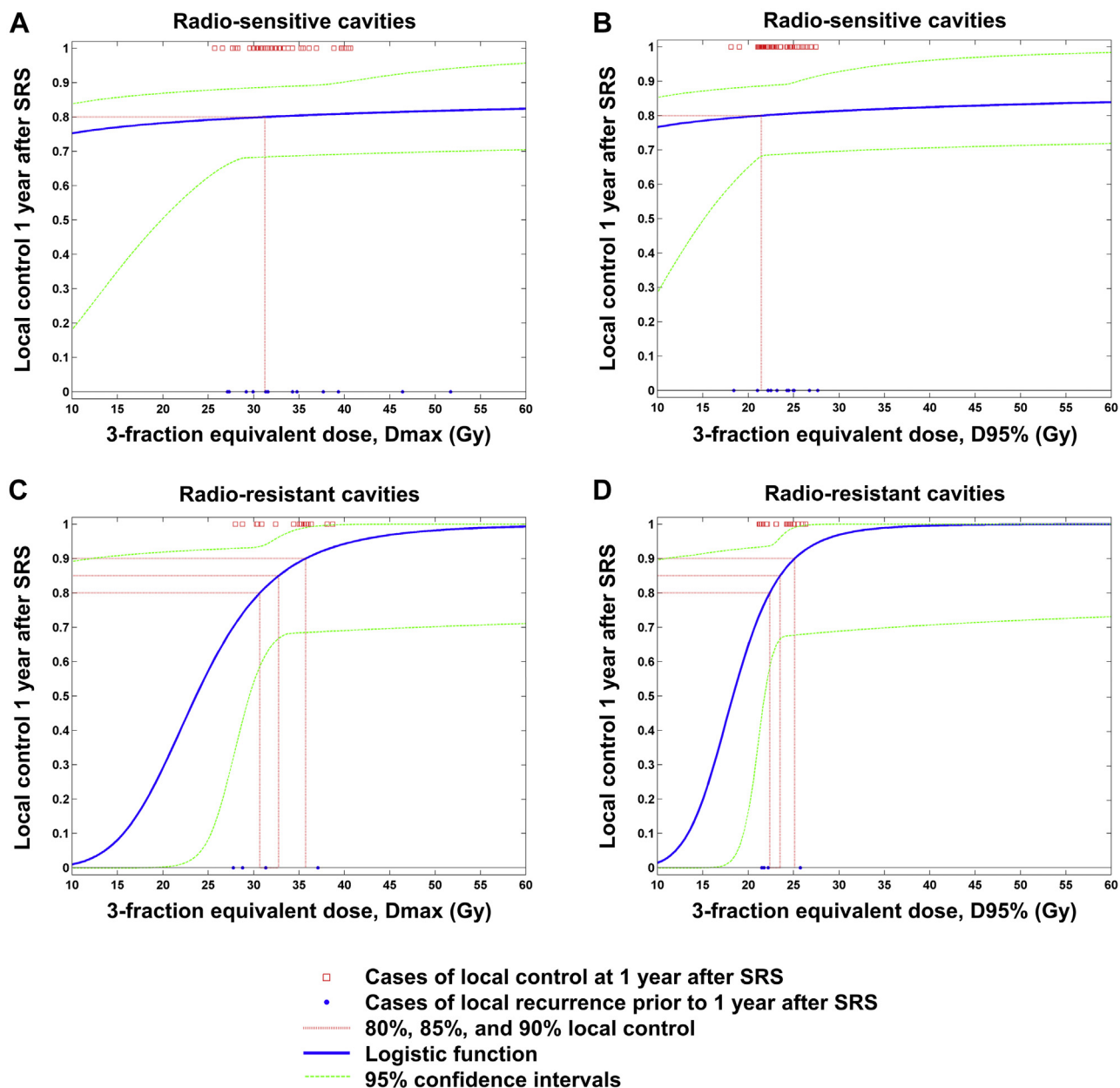
These potential benefits of higher radiation doses for large and radio-resistant resection cavities should be considered in the context of MTD established for single-fraction SRS.<sup>33</sup> Although single-fraction SRS may provide excellent local control for small targets, fractionated regimens may be required to optimize local control in patients with large radio-resistant cavities. Radiation Therapy Oncology Group 90-05 provided evidence that the MTD in a single fraction for targets <2 cm, 2 to 3 cm, and 3 to 4 cm in diameter are 24, 18, and 15 Gy, respectively.<sup>33</sup> In contrast, prospective data from Stanford indicates that the MTD for resection cavities between 2 and 4 cm in diameter is 30 Gy in 3 fractions,<sup>41</sup> which is a higher biologically equivalent dose than 18 or 15 Gy in 1 fraction. Taken together, these studies suggest that fractionation may enable the delivery of more effective radiation doses in patients with large resection cavities.

In addition, the presence of a meaningful dose-response with respect to D50%, D0.03 cm<sup>3</sup>, and D<sub>max</sub>

suggests that selective boosting of tumor subvolumes<sup>42</sup> may improve outcomes in patients with larger cavities and thus warrants further investigation. Several prior studies suggest that this approach is both technically feasible and safe in brain metastasis resection cavities<sup>43</sup> and other intracranial tumors.<sup>44</sup> Although delivering a boost to the residual gross tumor on anatomic MRI<sup>43</sup> represents a reasonable initial strategy, more accurate delineation of metabolically active tumor may require advanced imaging modalities.<sup>32,45</sup>

## Limitations

The limitations of this study are largely related to its single-institution, retrospective nature. First, despite the large size of the overall cohort, high rates of local control resulted in only 20 total cases of local tumor recurrence, which limits the statistical power of subgroup analyses. Thus, the findings of this study with respect to cavities of radio-resistant histology should be considered as hypothesis-generating rather than definitive. Second, local tumor recurrence was defined by clinical judgment when biopsy was not indicated or performed. In such circumstances, the ground truth cannot be definitively ascertained. Third, given that our institution was an early adopter of postoperative SRS to brain metastasis resection cavities, doses prescribed earlier in the study period were more conservative than our current institutional prescription of 24 to 27 Gy in 3 fractions. Although a wider range of prescriptions provides a statistical

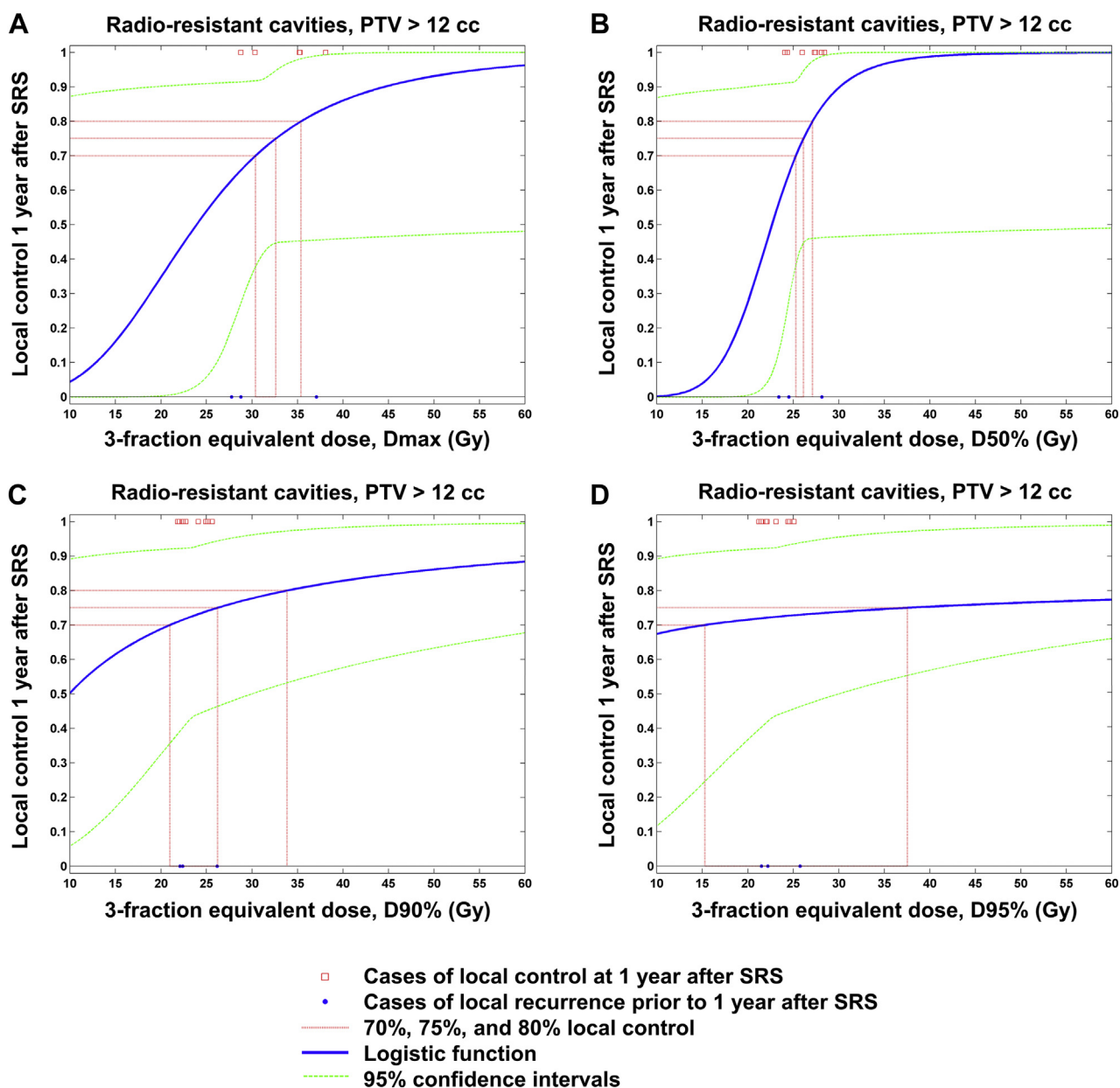


**Figure 2** Tumor control probability models for radio-sensitive and radio-resistant resection cavities. Logistic curves describe the relationship between local tumor control at 1 year after stereotactic surgery (SRS) and dose to the PTV in 3-fraction equivalents. Local control of radio-sensitive (A, B) and radio-resistant (C, D) cavities versus  $D_{\max}$  (A, C) and  $D_{95\%}$  (B, D) are shown. Similar dose-response relationships were detected for  $D_{0.03 \text{ cm}^3}$ ,  $D_{50\%}$ ,  $D_{90\%}$ , and  $D_{99\%}$  among radio-sensitive cavities (Fig E1) and radio-resistant cavities (Fig E2).

advantage, yielding richer dose-response models, overall local control rates in this population may not reflect current regimens. Nonetheless, this study was based on high-quality data obtained from one of the largest single-institution series of SRS for brain metastasis resection cavities described to date. All patients included in this study received follow-up MRI after SRS, and the median time to latest imaging follow-up was more than 12 months in patients who did not have local recurrence within the first year. Thus, this study represents an

important contribution to the literature despite its limitations.

From a broader perspective, this study suggests that higher doses may yield superior local control for large and radio-resistant cavities but was not intended to rigorously evaluate the corresponding risk of adverse effects. Our research group previously performed normal tissue complication probability modeling to assess the risk of symptomatic radionecrosis in a large cohort of patients who received SRS for intact and resected brain



**Figure 3** Tumor control probability models for large radio-resistant resection cavities (planning target volume [PTV] >12 cc). Logistic curves describe the relationship between local tumor control at 1 year after stereotactic surgery (SRS) and dose to the PTV in 3-fraction equivalents. D<sub>max</sub> (A), D<sub>50%</sub> (B), D<sub>90%</sub> (C), and D<sub>95%</sub> (D) are shown here. Additional models for D<sub>0.03</sub> cm<sup>3</sup> and D<sub>99%</sub> are provided (Fig E3).

metastases, which included the cases presented in this study.<sup>46</sup> This and similar studies have quantified the likelihood of neurotoxicity as a function of dose to the healthy brain parenchyma and have identified clinically meaningful benchmarks with implications for treatment planning.<sup>46-48</sup> Given the potential benefits of treating resection cavities with SRS at higher doses, particularly when employing fractionated regimens, continued quantification of adverse radiation effects is needed to assess the therapeutic index of this modality.

### Conclusions

This study presents the first quantitative evaluation of tumor control probability as a function of radiation dose after SRS for brain metastasis resection cavities. Consistent with the literature, larger cavities in this cohort were at greater risk of local recurrence. Tumor control probability modeling suggested that higher radiation doses were associated with substantially greater rates of local control, particularly among resection cavities of radio-resistant



histology but not among cavities of radio-sensitive histology. Given established maximum tolerated doses for single-fraction treatments,<sup>33</sup> these data suggest that, although single-fraction SRS may provide excellent local control when treating small targets, fractionated regimens may be required to optimize local control in patients with large radio-resistant cavities.

## Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2020.06.007>.

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