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Original Article

Dosimetric predictors of toxicity for brainstem metastases and AVMs treated with stereotactic radiosurgery: An international, multi-institutional analysis

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ABSTRACT

Background: There are limited data on dosimetric predictors of radiation-induced changes (RICs) for brainstem metastases or arteriovenous malformations (AVMs) following single-fraction stereotactic radiosurgery (SRS).
Methods: We examined a multi-institutional cohort of patients with brainstem metastases or AVMs treated with SRS. We evaluated predictors of RICs graded per CTCAE(Common Terminology Criteria for Adverse Events), including D5%, D95%, D0.03 cc, and D0.5 cc (brainstem minus lesion). Univariate logistic regressions were initially performed with independent variables trending towards significance included on multivariate logistic regression.
Results: A total of 124 brainstem lesions treated with SRS were analyzed (21 AVMs and 103 metastases). The median prescription dose was 16 Gy(range: 13–23 Gy), and the median treatment volume was 0.48 cc(range: 0.002–11.19 cc). The incidence of RICs was 9.7 % (with 3/12 being Grade 3–4 and no Grade 5). All cases occurred in brainstem metastases, with no cases among those of the midbrain-pons transition. Treatment volumes $\geq$ 1cc were correlated with a higher symptomatic RIC incidence(6/57 vs. 6/65; $p = 0.04$). Notably, all RIC cases had a D0.5 cc $\geq$ 15 Gy(12/87 vs. 0/32). Both D5%$\geq$6 Gy(9/55 vs. 3/69; $p = 0.04$) and D95%$\geq$1 Gy(7/31 vs. 5/93; $p = 0.01$) were significantly correlated with higher incidence of RICs and D0.03 cc $\geq$ 22 Gy was correlated with a lower risk(2/61 vs. 9/63; $p = 0.03$). On MVA, D0.03 cc $\geq$ 22 Gy remained a significant predictor of a lower incidence of RICs(odds ratio = -1.72 (95 % CI: −3.32 to −0.12; $p = 0.04$).

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Conclusions: Incidence of RICs was low following SRS for brainstem metastases and AVMs. We recommend optimizing radiosurgical plans for D0.5 cc < 15 Gy with consideration of D5% and D95%, with less emphasis on D0.03 cc to allow to meet the former metrics as feasible.

Introduction

Brain metastases are a source of significant morbidity and mortality in the United States [1–4]. The incidence of brain metastases is expected to continue to rise due to improving imaging technologies and novel targeted systemic therapies resulting in longer disease courses of patients with metastatic disease. Brainstem arteriovenous malformations (AVMs) are also challenging intracranial vascular malformations that are associated with significant morbidity and even mortality secondary to hemorrhagic events from the AVM nidus. Of note, brainstem metastases and AVMs may pose a disproportionate driver of impacts on quality-of-life given their eloquent location and high propensity for neurologic dysfunction.

Stereotactic radiosurgery (SRS) has emerged as a preferred treatment modality for patients with brain metastases given less neuro-cognitive toxicity and similar local control (LC) compared to whole brain radiation therapy (WBRT) [5,6]. Notably, brainstem metastases account for a minority of cases (roughly 4–7 % of metastases to the brain and 2–6 % of intracranial AVMs), and, as resection is not an option, SRS is often employed [7–10]. However, brainstem metastases and AVMs have often been excluded from prospective trials of SRS, limiting robust evaluation of relevant toxicities. A previous systematic review and *meta*-analysis established the efficacy of SRS for brainstem metastases and low rates of severe radiation induced changes (RICs) [9]. Also, a previous multi-institutional report also noted similar favorable LC and a relatively low rate of Grade 3 or greater toxicities [11].

However, there is limited data on dosimetric predictors of toxicity outside of QUANTEC constraints (maximum brainstem dose of 12.5 Gy), that are even more limited with respect to brainstem metastases and arteriovenous malformations (AVMs) [12]. A recent single institution experience of patient with brainstem metastases and AVMs within or abutting the brainstem noted that the brainstem is able to tolerate maximum doses beyond 12.5 Gy with minimal toxicity and that doses to higher volumes of brainstem (such as mean brainstem dose and D_5% and D_{95}%) were associated with higher rates of clinical complications [13]. Notably, the D_X% (Gy) represents the highest dose delivered to X% of the brainstem volume subtracting the lesion volume from the brainstem volume). With regards to AVMs, recent examinations of patients with brainstem AVMs treated with SRS have noted favorable obliteration rates but without significant data on long-term toxicities and relevant dosimetric predictors of toxicity [14].

Given limited data in the space of SRS and modern dosimetric predictors of severe brainstem toxicity, we aimed to examine the International Radiosurgery Research Foundation (IRRF) cohort to evaluate incidence of both asymptomatic and symptomatic RICs after SRS and identify potential planning goals for optimal radiosurgical planning.

Materials and Methods

This project was initially reviewed by the IRRF review committee and after approval participating centers queried each of their own registries (with institutional IRB approval) for patients with brainstem metastases or AVMs managed with single fraction SRS that had clinical and radiographic follow-up for assessment of RICs. Other data that was requested and collected included but was not limited to patient age, performance status at diagnosis, at time of SRS and at last follow-up, systemic therapy utilized (and timing of systemic therapy in relation to SRS), disease, lesion location (midbrain, pons, medulla, or midbrain pons or pons-medulla transitions), gross tumor volume (GTV), planning target volume (PTV, if applicable if an expansion margin was utilized), marginal prescription dose (MPD), isodose line, maximum dose, and dosimetric brainstem information (D0.03 cc, D0.5 cc D_5% and D_{95}% of the brainstem, mean brainstem dose, and volume of the normal brainstem receiving 12 Gy (V_{12Gy}).

Inclusion criteria were patients with brainstem metastases or AVMs, those with at least 6 months of clinical and radiographic follow-up for assessment RICs, with dosimetric data (including D0.03 cc, D0.5 cc, D_5% and D_{95}% of the brainstem, and mean brainstem dose),where each of these were total brainstem minus lesion volume, and those with information on treatment planning (margin prescription dose, isodose, and target volume).

Radiosurgical approach

To allow for uniform dosimetric comparisons, only patients treated with single fraction SRS were included in this analysis. Planning of SRS was per institutional guidelines but included use of magnetic resonance imaging (MRI) of the brain for brain metastases and diagnostic cerebral angiogram and computed tomography / CT angiography (CTA) or magnetic resonance/ MR angiography (MRA) for AVMs with dose selection per institutional preference per planning by the treating radiation oncologist, neurosurgeon, and medical physicist.

Clinical and radiologic follow up and definition of endpoints

RICs were characterized based on post-SRS imaging on MRI with or without perfusion imaging, PET (with standardized uptake values (SUV)), or MRI spectroscopy (with choline/creatinine ratios) with findings including but not limited to contrast enhancement and perilesional edema, or specific patterns such as a “soap bubble” or “Swiss cheese”, as per local consensus per prior IRRF analyses [15]. CTCAE 5.0 Grade definitions were utilized to define RIC grading (1 – asymptomatic; 2 – mild or moderate symptoms requiring non-invasive management; 3 – medically significant and disabling symptoms requiring hospitalization; 4 – life threatening consequences; 5 – related death). Notably, the vast majority of centers utilized MRI Brain with and without contrast with subsequent perfusion imaging to define radionecrosis, with low cerebral blood volumes with increased enhancement and/or FLAIR changes in the field of SRS deemed to be consistent with radionecrosis.

Statistical methods

Logistic regression was utilized to assess for correlations between various independent variables, most notably age, KPS, receipt of concurrent immunotherapy, marginal prescription dose, maximum dose, GTV/PTV, dosimetric factors including D0.03 cc, D0.5 cc, $D_{5\%}$ and $D_{95\%}$ of the brainstem, and mean brainstem dose) and the dependent variables of both asymptomatic and symptomatic RIC incidence. Initially, univariate analysis (UVA) was performed with employment of a forward selection model with variables found to have $p \leq 0.10$ then included on multivariate logistic regression (MVA). Differences were considered statistically significant if $p \leq 0.05$ on multivariate logistic regression. We utilized Stata 14.0 (College Station, TX) for statistical analysis.

Results

Summary of patient cohort

After our query of IRRF centers, we identified a total of 124 brainstem metastases and AVMs that were treated with single fraction SRS

and met study inclusion/exclusion criteria. A summary of the cohort analyzed can be found in Table 1. Twenty-one of the lesions included in the cohort were AVMs and 103 were brainstem metastases. The median age was 59 (range: 13–87) with a median KPS of 85 % (range: 40–100 %). For patients with AVMs, the age range was 13 to 72 and for patients with metastases the age range was 38 to 87. There were 69 female patients and 55 male patients. The most common locations of lesions were the midbrain (26 lesions) and pons (69 lesions) with other sites the medulla (10 lesions), midbrain-pons transition (11 lesions), and pons-medulla transition (8 lesions). Of the brain metastasis cohort, the most common primary sites were non-small cell lung cancer (37 metastases), breast cancer (22 metastases), melanoma (12 metastases), small-cell lung cancer (11 metastases), and renal cell carcinoma (9 metastases). The cumulative brain metastasis volume was 1.7 cc (range: 0.01–73.7 cc) in the brain metastasis cohort. Of the AVM cohort, the median AVM volume was 0.36 cc (range: 0.009–8.0 cc). Of the brain metastasis cohort, 71/103 patients received concurrent systemic therapy (32 with cytotoxic chemotherapy, 17 with immunotherapy, 15 with targeted therapies, and 7 with a combination of cytotoxic chemotherapy and immunotherapy).

Summary of SRS planning and dosimetry

A summary of relevant SRS planning as well as dosimetric data can be found in Table 2. The median MPD was 16 Gy (range: 13–23 Gy) with a median isodose prescription of 50 % (range: 40–98 %). Among AVMs, the median MPD was 16 Gy (range: 14–23) and among brainstem metastases the median PTV was also 16 Gy (range: 13–22 Gy). The median PTV was 0.48 cc (range: 0.002–11.19 cc). The median margin expansion employed to generate the PTV was 0.5 mm (range: 0–2 mm), with all patients being treated with Gamma Knife. Among AVMs, the median PTV was 0.9 cc (range: 0.026–11.2 cc), and the median PTV among brainstem metastases was 0.4 cc (range: 0.002–9.5 cc). The median V_{12Gy} including and excluding the target volume were 3.9 cc (range: 0.05–80.6 cc) and 2.2 cc (range: 0.01–72.1 cc), respectively. The median mean brainstem dose was 2.4 Gy (range: 0.1–7.5 Gy). The median D0.03 cc and D0.5 cc brainstem were 20.7 Gy (range: 5.8–66.5 Gy) and 12.7 Gy (range: 0.5–27.6 Gy), respectively. The median D_5% and D_{95}% were 5.1 Gy (range: 0.05–48) and 0.3 Gy (range: 0.03–18 Gy), respectively. Follow-up and overall survival for the entire cohort and for those with brainstem metastases only can be found in Fig. 1 and Fig. 2, respectively. The median follow-up for patients with brainstem metastases and across the entire cohort was 20.6 months and 24.4 months. (range of 1–143 months for both).

Table 1
Descriptive statistics of cohort.

Variable	
Gender	55 male patients 69 female patients
Median Age (years) (range)	59 (13–78)
Median KPS (%) (range)	85 % (40–100 %)
Location of lesion	*Pons* – 69 *Midbrain* – 26 *Midbrain to pons transition* – 11 *Medulla*– 10 *Pons to medulla transition* – 8
Primary histology (for brain metastasis cohort)	*Non-small cell lung cancer* – 37 *Breast* – 22 *Malignant melanoma* – 12 *Small-cell lung cancer* – 11 *Renal cell carcinoma* – 9 *Other* – 33
Cumulative brain metastasis volume (cc) (range) (for brain metastasis cohort)	1.7 (0.01–73.7)
Median AVM volume (cc) (range)	0.36 (0.009–8.0)

*KPS = Karnofsky Performance Status; AVM = arteriovenous malformation

Table 2
Descriptive statistics of SRS planning and relevant dosimetry.

Variable	
Median target volume (cc) (range)	0.48 (0.002–11.2)
Median target volume (cc) (range) (brain metastasis cohort)	0.4 (0.002–9.5)
Median target volume (cc) (range) (AVM cohort)	0.9 (0.026–11.2)
Median MPD (Gy) (range)	16 (13–23)
Median MPD (Gy) (range) (brain metastasis cohort)	16 (13–22)s
Median MPD (Gy) (range) (AVM cohort)	16 (14–23)
Median V_{12Gy} (including target volume) (cc) (range)	3.9 (0.05–80.6)
Median V_{12Gy} (excluding target volume) (cc) (range)	2.2 (0.01–72.1)
Median mean brainstem dose (Gy) (range)	2.4 (0.1–7.5)
Median D0.03 cc brainstem (Gy) (range)	20.7 (5.8–66.5)
Median D0.5 cc brainstem (Gy) (range)	12.7 (0.5–27.6)
Median D_5% (Gy) (range)	5.1 (0.05–48)
Median D_{95}% (Gy) (range)	0.3 (0.03–18)

*AVM = arteriovenous malformation; MPD = marginal prescription dose; D_X% = the highest dose delivered to X% of the brainstem volume and mean brainstem volume subtracting the lesion volume from the dose/brainstem volume; V_{12Gy} = volume of the normal brainstem receiving 12 Gy;

Radiation induced changes

Regarding both asymptomatic and symptomatic RICs, the overall incidence following SRS in the cohort was 12/124 (9.7 %). The CTCAE grading for these cases was one Grade 1, nine Grade 2, two Grade 3, one Grade 4, and no Grade 5 toxicities (i.e. 11 cases of symptomatic imaging changes and 1 that was a case of asymptomatic imaging changes). All Grade 2 and above cases initially received dexamethasone, with 6/9 of the Grade 2 incidences resolving after an initial dexamethasone burst (ie. requiring a short dexamethasone taper) and 3/9 requiring additional dexamethasone bursts. Both Grade 3 cases and Grade 4 cases were managed with Avastin and requiring chronic medical management. Notably, all of these cases occurred in patients with brainstem metastases with no cases of treated AVMs. Also, there were no cases of adverse clinical events for lesions located in the midbrain to pons transition (0/10). Regarding incidence of RICs, there were no lesion or patient characteristics that were significantly associated with this other lesion location. For symptomatic RICs, we noted that PTV volumes $\geq$ 1cc were correlated with a higher incidence of toxicities (6/57 vs. 6/65; $p = 0.04$) with no other lesion or patient characteristics associated with this. Concurrent systemic therapy was also not significantly associated with a higher incidence of RICs.

With respect to dosimetric predictors of toxicity, we found that all incidences of asymptomatic and symptomatic RICs occurred when D0.5 cc $\geq$ 15 Gy (12/87 vs. 0/32). Given this collinearity, additional statistical testing (either Chi-Squared or logistic regression) was unable to be performed for this independent variable. We noted that both.

D5% $\geq$ 6 Gy (9/55 vs. 3/69; $p = 0.04$) and D95% $\geq$ 1 Gy (7/31 vs. 5/93; $p = 0.01$) were significantly correlated with higher incidence of RICs. Interestingly,

D0.03 cc $\geq$ 22 Gy was significantly correlated with a lower risk of RICs (2/61 vs. 9/63; $p = 0.03$). On MVA, including the above significant dosimetric predictors initially noted on UVA, D0.03 cc $\geq$ 22 Gy was a significant predictor of a lower incidence of RICs (odds ratio (OR) = -1.72 (95 % CI: −3.32 to −0.12; $p = 0.04$) whereasD5% $\geq$ 6 Gy ($p = 0.20$) and D95% $\geq$ 1 Gy ($p = 0.21$) were not significant. On examination of only symptomatic RICs, we did not find any significant dosimetric predictors of these events.

Discussion

Similar to general management of brain metastases and AVMs, given the risk of significant morbidity due to local disease progression, early intervention to prevent potential neurologic complications from both brainstem metastases and AVMs is usually recommended. However, with SRS there is a concern of a higher risk profile/incidence of RICs

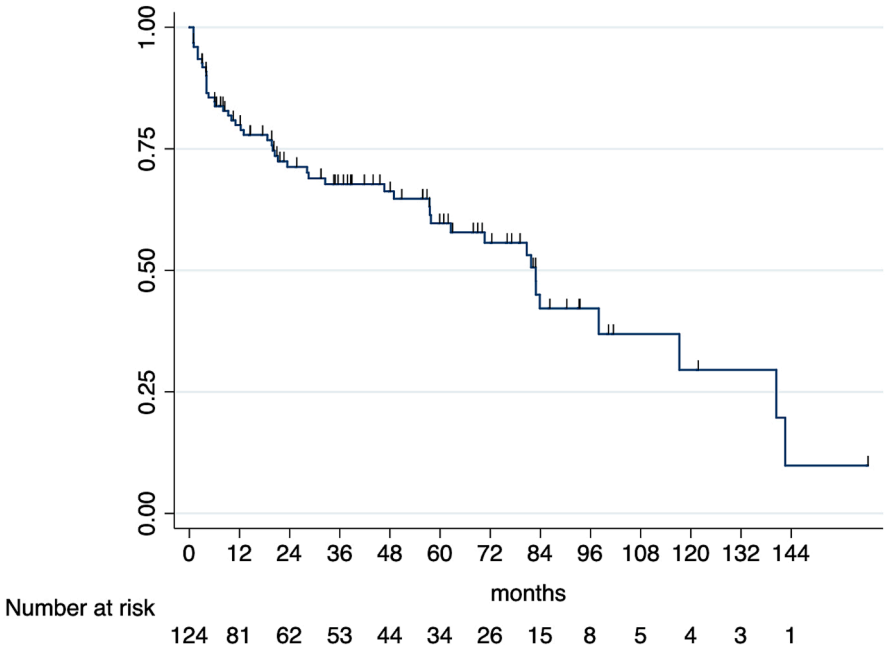


Fig. 1. Kaplan-Meier curve of overall survival for entire cohort.

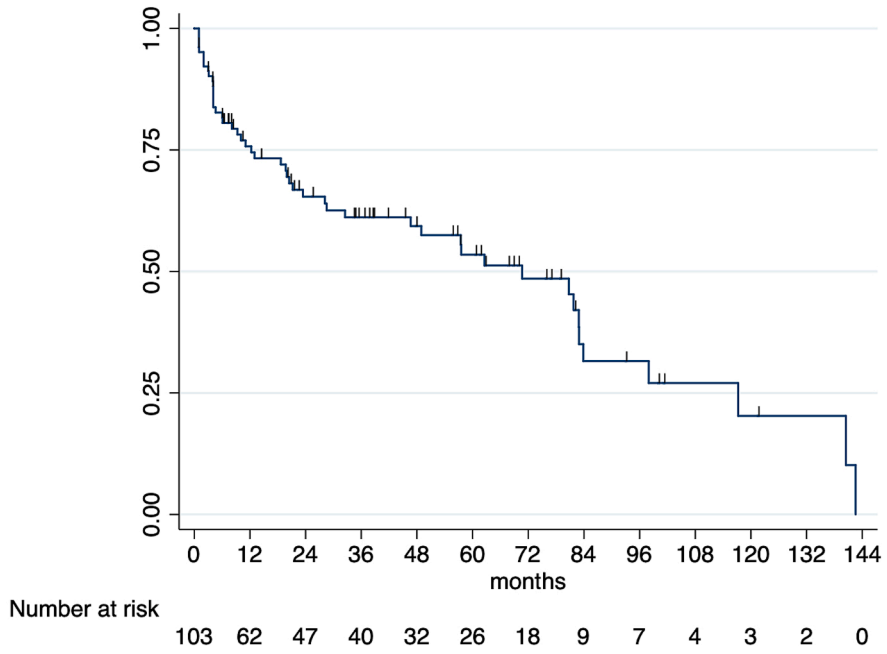


Fig. 2. Kaplan-Meier curve of overall survival for patients with brainstem metastases.

with SRS for lesions in this eloquent location with limited data to guide optimal SRS planning. Our real-world, international multi-institutional analysis noted a favorable, low incidence of RICs of roughly 10 % following SRS, with 2.5 % total being Grade 3–4 and with no Grade 5 toxicities. Interestingly, all cases of RICs were noted to be in the brain metastasis cohort. Dosimetric predictors of RICs were noted to be D0.5 cc $\geq$ 15 Gy and D0.03 cc $<$ 22 Gy, with D5% $\geq$ 6 Gy, and D95% $\geq$ 1 Gy also significant on initial UVA. In tandem, our findings suggest that high dose low volume bath seems to be a smaller driver of RICs rather than higher volume and low to intermediate dose volume, which suggests that aggressive isodose prescriptions for sharp dose fall-offs (ie. sharp penumbra with lower isodose prescription/higher max point doses in lesions) seems to be the optimal radiosurgical approach for these challenging scenarios.

Our findings with respect to the incidence of severe RICs are very similar to prior analyses. The largest systemic review and *meta*-analysis on the topic by Chen et al. examined 32 studies with close to 1600 brainstem metastases treated with single-fraction SRS with a median MPD of 16 Gy. They noted a Grade 3–5 toxicity of 2.4 % (95 % CI: 1.5–3.7 %) with 31 of the 32 studies having information on this outcome [9]. A prior analysis by the IRRF of nearly 600 brainstem metastases by Trifiletti et al. with a median MPD of 16 Gy reported a higher Grade 3–5 toxicity rate of 7.4 %, with factors associated with a higher incidence being receipt of prior WBRT, larger tumor volumes, and higher MPDs [11]. Similar to our analysis, V_{12Gy} (including the GTV) was not found to be a significant predictor of RICs ($p = 0.06$) with the interquartile range

of MPDs associated with Grade 3–5 RICs being 17–19 Gy. There have also been analyses examining the use of fractionated SRS. An analysis by Kramer, et al., examined RN outcomes for patients with brainstem metastases following fractionated SRS of 30 Gy/6 fractions with CyberKnife prescribed to the 70 % isodoses line with a 1 mm PTV expansion. Following SRS, 8.2 % of patients had symptomatic (ie. CTCAE Grade 2 or greater) radionecrosis with a median follow-up of 27.3 months [17].

With regards to previous reports and predictors of brainstem toxicity following SRS, the initial QUANTEC effort recommended a maximum brainstem dose of 12.5 Gy, which with contemporary brainstem SRS dosing would be felt to pose a risk of inferior local control or obliteration for AVMs or control of brainstem metastasis [12]. The more recent HyTEC (High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic) effort noted V_{12Gy} as a driver of symptomatic RICs but without specific dosimetric data for brainstem metastases and AVMs [16]. A single institution analysis by Lehrer et al. of brainstem metastases or AVMs within or abutting the brainstem with a median MPD of 18 Gy (range: 13–25 Gy) noted asymptomatic and symptomatic RIC rates of roughly 28 % and 16 %, respectively. Higher mean brainstem doses, D5%, and D95% were correlated with increased incidences of asymptomatic RICs, and increasing D5% was significantly associated with an increased risk of symptomatic RICs [13]. Similar to our own analysis, we noted that D5% and D95% were significantly correlated on UVA with asymptomatic RICs and warrant evaluation in addition to standard high-dose, low-volume historical metrics.

Limitations.

There are a number of limitations that should be discussed in this analysis. The multi-institutional nature of this analysis introduces potential heterogeneity for a number of relevant clinical aspects of classification of RICs, notably potential varying institutional practices for diagnosis of RICs (MRI with perfusion imaging, MRI spectroscopy, PET imaging with fluciclovine, etc.). Some of these modalities are also limited in their utility for certain radiographic situations (i.e. MRI with perfusion imaging for medulla lesions). Also, given the rarity of brainstem metastases and AVMs and low incidence of RICs, there were a number of clinical and dosimetric situations that were unable to be addressed statistically due to co-linearity (ie. D0.5 cc and midbrain to pons locations). Also, given the poor prognosis associated with brainstem metastases, the shorter duration of follow-up and survival also resulted in shorter intervals during which patients were at risk of developing RN that may have led to a shorter incidence of RN events.

Conclusion

The incidence of RICs following SRS for brainstem is relatively low, thus suggesting that continued use of SRS for the indications of brainstem metastases and AVMs is warranted. We recommend keeping D0.5 cc $<$ 15 Gy and also evaluation of D0.03 cc (with less restriction of this above 22 Gy if necessary to meet the prior) also with consideration of D5% (aim of $<$ 6 Gy and D95% (aim of $<$ 1 Gy) to minimize the risk of RICs following SRS.

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Ethics: The procedures followed for the purposes of this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996 and 2000) of the World Medical Association.

CRediT authorship contribution statement

Raj Singh: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Samantha Dayawansa:** Writing – review & editing, Data curation. **Duy Pham:** Writing – review & editing, Data curation. **Georgios Mantziaris:** Writing – review & editing, Data curation. **Selcuk Peker:** Writing – review & editing, Data curation. **Yavuz Samanci:** Writing – review & editing, Data curation. **Ali Haluk Duzkalir:** Writing – review & editing, Data curation. **David Mathieu:** Writing – review & editing, Data curation. **Anne-Marie Langlois:** Writing – review & editing, Data curation. **Molly L. Egnot:** Writing – review & editing, Data curation. **Ronald E. Warnick:** Writing – review & editing, Data curation. **Herwin Speckter:** Writing – review & editing, Data curation. **Erwin Lazo:** Writing – review & editing, Data curation. **Laura Mendez:** Writing – review & editing, Data curation. **Angel I. Blanco:** Writing – review & editing, Data curation. **Mark J. Amsbaugh:** Writing – review & editing, Data curation. **Collin Liu:** Writing – review & editing, Data curation. **Andrea Becerril-Gaitan:** Writing – review & editing, Data curation. **Yoshua Esquenazi:** Writing – review & editing, Data curation. **Ching-Jen Chen:** Writing – review & editing, Data curation. **Peter Zaki:** Writing – review & editing, Data curation. **Yun Liang:** Writing – review & editing, Data curation. **Rodney Wegner:** Writing – review & editing, Data curation. **Manjul Tripathi:** Writing – review & editing, Data curation. **Zhishuo Wei:** Writing – review & editing, Data curation. **Shivani A. Jajoo:** Writing – review & editing, Data curation. **Ajay Niranjan:** Writing – review & editing, Data curation. **L.Dade Lunsford:** Writing – review & editing, Data curation. **Joshua D. Palmer:** Writing – review & editing, Supervision, Conceptualization. **Jason P. Sheehan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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