JNS

CLINICAL ARTICLE

J Neurosurg 144:200–205, 2026

Posttreatment toxicity following single-fraction versus multifraction hypofractionated stereotactic radiosurgery for larger meningiomas

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OBJECTIVE Stereotactic radiosurgery (SRS) has been used to manage patients with intracranial meningioma with contraindications to resection. Limitations to SRS traditionally include tumors > 3 cm due to the risk of posttreatment toxicity. Hypofractionated SRS (hSRS) has been proposed as an alternative for tumors exceeding volume constraints for single-fraction SRS, although how hypofractionation affects the volume versus toxicity relationship has not been reported. Thus, the authors conducted a single-institution retrospective analysis of the medical records of patients receiving single-fraction SRS or multifraction hSRS for large (> 2 cm) meningiomas to assess the effect of hypofractionation on the likelihood of posttreatment toxicity.

METHODS Patients were identified using the Wake Forest University Department of Radiation Oncology prospectively administered Gamma Knife database. Patients were included if they had single-fraction SRS or multifraction hSRS for a diagnosis of meningioma that was > 2 cm. Analysis was limited to tumor volumes between 2.7 and 49.3 cm^3, the overlapping range shared by those undergoing hSRS or SRS. Electronic medical records were used to determine patient and tumor characteristics and clinical outcomes.

RESULTS A total of 121 SRS cases with a median dose of 12 Gy and 51 hSRS cases with a median dose of 20 Gy with tumor volumes between 2.7 and 49.3 cm^3 were identified and included in the analysis. The probabilities of freedom from local failure at 1, 3, and 5 years were 87.0%, 79.0%, and 63.6%, respectively, for patients receiving single-fraction SRS and 96.0%, 91.0%, and 91.0%, respectively, for patients receiving multifraction hSRS. The probabilities of overall survival at 1, 3, and 5 years were 97.5%, 79.7%, and 72.6%, respectively, for patients receiving single-fraction SRS and 85.5%, 80.9%, and 76.4%, respectively, for patients receiving multifraction hSRS. Eighteen (14.9%) of 121 patients receiving single-fraction SRS experienced Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 toxicity, and 12 (23.5%) of 51 patients receiving multifraction hSRS experienced CTCAE grade ≥ 2 toxicity.

CONCLUSIONS When controlling for tumor volume, despite higher treatment doses in the hSRS group relative to the SRS group, posttreatment toxicity was not significantly different between the groups, and freedom from local failure was improved in the hSRS group. For patients with larger meningiomas, multifraction hSRS may help to limit the risk of posttreatment edema and toxicity, while maintaining acceptable freedom from local failure.

https://thejns.org/doi/abs/10.3171/2025.4.JNS242824

KEYWORDS meningioma; radiation toxicity; stereotactic radiosurgery; hypofractionation

STEREOTACTIC radiosurgery (SRS) is an effective, noninvasive management option for patients with intracranial meningioma.[1] Contraindications to resection for meningioma have included tumors overlying or involving eloquent brain and tumors of the cavernous sinus. In addition, tumors abutting or encasing major vessels such as a dural sinus may not be resectable in their entirety.[2] Such cases in which tumors cannot be resected completely may instead be candidates for SRS. Limitations to SRS have traditionally included tumors > 3 cm due to the risk

ABBREVIATIONS CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external-beam radiotherapy; hSRS = hypofractionated SRS; SRS = stereotactic radiosurgery.

SUBMITTED November 21, 2024. **ACCEPTED** April 18, 2025.
INCLUDE WHEN CITING Published online August 8, 2025; DOI: 10.3171/2025.4.JNS242824.

of posttreatment toxicity and tumors in close proximity to the optic nerves due to the risk of optic neuropathy.[3]

Hypofractionated SRS (hSRS) has been proposed as an alternative to SRS in the setting of tumors that have exceeded volume constraints for single-fraction SRS or are in close proximity to the optic nerves.[4] Early series suggest that there may be a decreased risk of posttreatment toxicity with hSRS as compared with single-fraction SRS, particularly for tumors that are in the upper limit of the dose-volume tolerances for SRS.[5] It has not yet been reported, however, how hypofractionation affects the volume versus toxicity relationship when treating larger meningiomas.

To that end, we conducted a single-institution retrospective analysis of the medical records of patients receiving either single-fraction SRS or multifraction hSRS for meningiomas > 2 cm with the intent of assessing the effect of hypofractionation on the likelihood of posttreatment edema and toxicity.

Methods

Data Acquisition

This study was approved by the Wake Forest University School of Medicine Institutional Review Board. Patients were identified using the Wake Forest University Department of Radiation Oncology prospectively administered Gamma Knife database. Patients were included in the study if they had either single-fraction Gamma Knife SRS or multifraction hSRS for a diagnosis of meningioma that was > 2 cm. Analysis was limited to those cases with tumor volumes between 2.7 and 49.3 cm^3, the overlapping range shared by those undergoing hSRS or SRS. Electronic medical records were used to determine patient and tumor characteristics as well as to determine clinical outcomes. Patients with meningioma of any histological grade or with presumed meningioma (without biopsy confirmation) were included in the study. All patients triaged to treatment had enlarging tumor size with or without worsening symptoms.

SRS and hSRS

Single-fraction SRS was performed on the Leksell Gamma Knife U (1999–2003), C (2004–2008), Perfexion (2009–2016), and ICON (2017–2023) models (Elekta). A Leksell 4-pin stereotactic headframe (Elekta) was placed by a neurosurgeon using local anesthetic on the morning of treatment. High-resolution MRI (GE HealthCare Technologies) was performed with the stereotactic headframe in place.

Multifraction hSRS was performed on the Perfexion (2013–2016) using the eXtend bite-block palatal vacuum immobilization system (Elekta), and on the ICON (2017–2023) using a rigid aquaplast mask, cone beam CT positional confirmation, and intrafractional monitoring of motion using the High Definition Motion Management system (Elekta) via infrared camera tracking of reflective fiducials.

Treatment planning was performed on the GammaPlan system (Elekta) for both SRS and hSRS cases. The median prescribed margin dose for SRS was 12.0 Gy (IQR 12.0–13.0 Gy). The median prescribed margin dose for hSRS was 20.0 Gy in 4 fractions (5 Gy/fraction; IQR 20.0–20.0 Gy). Prior to the advent of multifraction Gamma Knife radiosurgery in 2013, patients were offered single-fraction SRS at the discretion of the multidisciplinary team consisting of a neurosurgeon and radiation oncologist, and the dose to the tumor was commonly decreased to account for a risk of radiation necrosis if the lesion was > 3 cm. After hSRS became available in 2013, patients with large tumors or those with tumors too close to the optic nerves such that we could not meet an 8-Gy point dose maximum constraint in a single-fraction plan were treated with hSRS. Patients with tumors > 3 cm (approximately 20 cm^3) were generally offered hSRS instead of single-fraction SRS to potentially mitigate the risk of posttreatment toxicity after review by both a neurosurgeon and a radiation oncologist. Pretreatment edema and tumor location did not play a significant role in treatment decision-making in this described population of patients.

TABLE 1. Demographic and treatment characteristics of those receiving hSRS or SRS for large meningiomas

Variable	hSRS	SRS	p Value*
Total pts	51	121	
Sex			0.999
Male	15 (29.4)	37 (30.6)	
Female	36 (70.6)	84 (69.4)	
Age, yrs	67.0 (51.0–77.0)	63.9 (47.7–73.3)	0.115
Tumor vol, cm^3	15.9 (10.0–20.3)	6.1 (4.3–10.2)	<0.001
Treatment dose, Gy	20.0 (20.0–20.0)	12.0 (12.0–13.0)	<0.001
Pretreatment edema			0.425
Yes	14 (27.5)	25 (20.7)	
No	37 (72.5)	96 (79.3)	
Any toxicity			0.217
Yes	15 (29.4)	32 (26.4)	
No	36 (70.6)	89 (73.6)	
CTCAE grade 1 toxicity			0.085
Yes	3 (5.9)	14 (11.6)	
No	48 (94.1)	107 (88.4)	
CTCAE grade ≥2 toxicity			0.097
Yes	12 (23.5)	18 (14.9)	
No	39 (76.5)	103 (85.1)	
Race/ethnicity			0.999†
White	42 (82.4)	106 (87.6)	
Black	5 (9.8)	14 (11.6)	
Asian	2 (3.9)	0	
Hispanic	2 (3.9)	0	
Other	0	1 (0.8)	

Pt = patient.
Values are given as number of patients (%) or median (IQR) unless otherwise indicated.
* Mann-Whitney U-test for continuous variables. Chi-square test for categorical variables.
† White versus all other race/ethnicity categories.

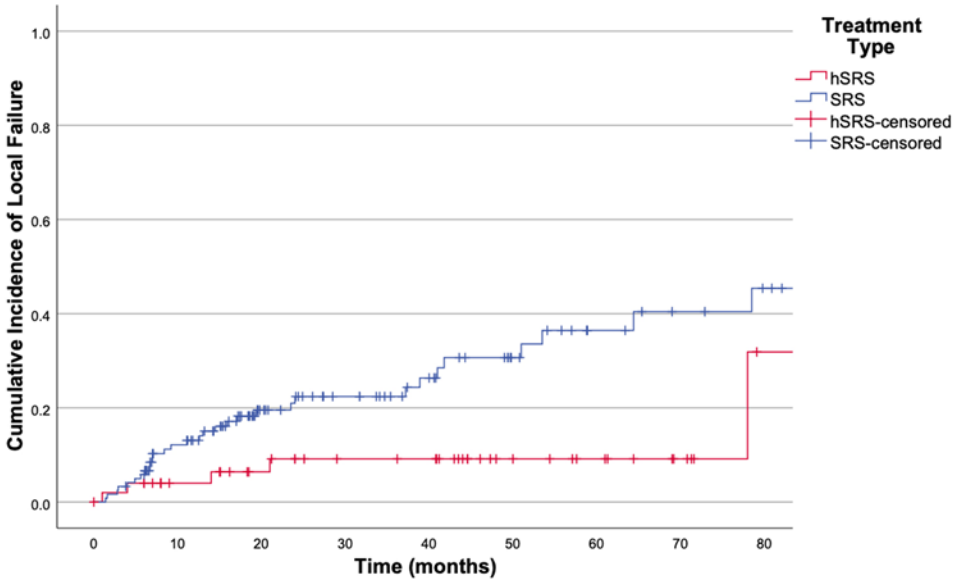

FIG. 1. Kaplan-Meier curve depicting the cumulative incidence of local failure in patients undergoing hSRS and SRS. The cumulative incidence of local failure was higher in the SRS group compared with the hSRS group ($p = 0.034$). The table is truncated at 80 months, when < 10% of patients remained. Figure is available in color online only.

Patient Follow-Up and Toxicity Assessment

Patients were generally followed up with MRI of the brain 6 months after initial SRS or hSRS treatment, and then annually for the first 5 years after treatment. Visits were spaced out to become less frequent thereafter based on the neurosurgeon's discretion. The Common Terminology Criteria for Adverse Events (CTCAE) toxicity scale version 5.0 was used to assess for toxicity: grade 1 toxicity represented asymptomatic edema; grade 2, moderate symptoms; grade, 3 severe symptoms; grade 4, life-threatening symptoms; and grade 5, death. Patient posttreatment imaging was additionally reviewed to assess for posttreatment edema. Local failure was defined as evidence of lesion growth on brain MRI with and without contrast following SRS or hSRS treatment, not attributable to postradiation changes.

Statistical Analysis

Descriptive statistics are summarized as frequency (percentage) or median (IQR). Two-tailed p values < 0.05 were considered statistically significant for this study. Generalized linear models using the binomial family with logit link function were constructed to predict the probability of any toxicity and CTCAE grade ≥ 2 toxicity. Predictors of treatment type (SRS vs hSRS), tumor volume (continuous), treatment dose, race (White/non-White), age (continuous), and sex (male/female) were considered in the models. Treatment type, tumor volume, and treatment dose remained after model fitting using Akaike's information criterion. Residuals were examined to confirm adequacy of the models. The overall cumulative incidence of failure was modeled with death as a competing risk and censored at the last follow-up date if no prior event occurred. Estimates for freedom from local failure and overall survival were obtained with product-limit survivor functions via the Kaplan-Meier method. Gray's test on the cumulative incidence of failure function was used to investigate differences between treatment types, whereas the log-rank test was used for overall survival. Analysis was conducted using SAS version 9.4 (SAS Institute), R version 4.4.1 (R Foundation for Statistical Computing), and RStudio version 2024.04.2 (Posit).

Results

Patient Population

From 1999 to 2011, 202 patients were treated with single-fraction SRS with a median dose of 12 Gy for intracranial meningiomas > 2 cm in the greatest dimension. From 2013 to 2023, 56 patients were treated with multifraction hSRS with a median dose of 20 Gy for intracranial meningiomas > 2 cm in the greatest dimension. A subgroup of 121 SRS and 51 hSRS cases with tumor volumes between 2.7 and 49.3 cm^3 were included in the analysis. Patient characteristics are summarized in Table 1.

Local Control

The probabilities of freedom from local failure at 1, 3, and 5 years were 87.0%, 79.0%, and 63.6%, respectively, for patients receiving single-fraction SRS and 96.0%, 91.0%, and 91.0%, respectively, for patients receiving multifraction hSRS. SRS cases had a higher cumulative incidence of local failure than hSRS cases ($p = 0.034$) (Fig. 1).

Overall Survival

The probabilities of overall survival at 1, 3, and 5 years were 97.5%, 79.7%, and 72.6%, respectively, for patients receiving single-fraction SRS and 85.5%, 80.9%, and 76.4%, respectively, for patients receiving multifraction hSRS. There was no difference between SRS and hSRS cases in

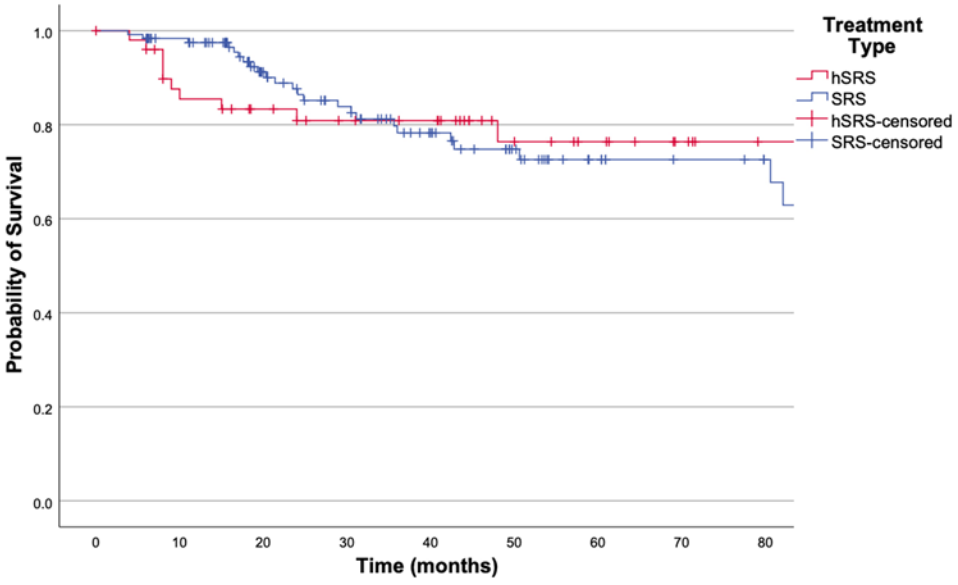

FIG. 2. Kaplan-Meier curve depicting the overall survival of patients undergoing hSRS and SRS. There was no difference in probability of survival between the two groups (p = 0.855). The table is truncated at 80 months, when < 10% of patients remained. Figure is available in color online only.

the probability of overall survival (p = 0.855) (Fig. 2). No patient death was suspected secondary to tumor progression, and no patient death was secondary to toxicity.

Posttreatment Toxicity

Thirty-two (26.4%) of 121 patients receiving single-fraction SRS experienced any CTCAE grade toxicity, while 18 (14.9%) of 121 patients receiving single-fraction SRS experienced CTCAE grade ≥ 2 toxicity. Fifteen (29.4%) of 51 patients receiving hSRS experienced any CTCAE grade toxicity, while 12 (23.5%) of 51 patients receiving multifraction hSRS experienced CTCAE grade ≥ 2 toxicity. The predicted probabilities for any grade toxicity are plotted in Fig. 3. As tumor volume increases, there is a statistically significant increase in the risk of any toxicity (p = 0.022) and grade ≥ 2 toxicity (p = 0.009) for both treatment groups. There is no difference in the overall risk of any toxicity or grade ≥ 2 toxicity between SRS and hSRS when controlling for tumor volume and dose (p = 0.217 and p = 0.097, respectively). Tumor features such

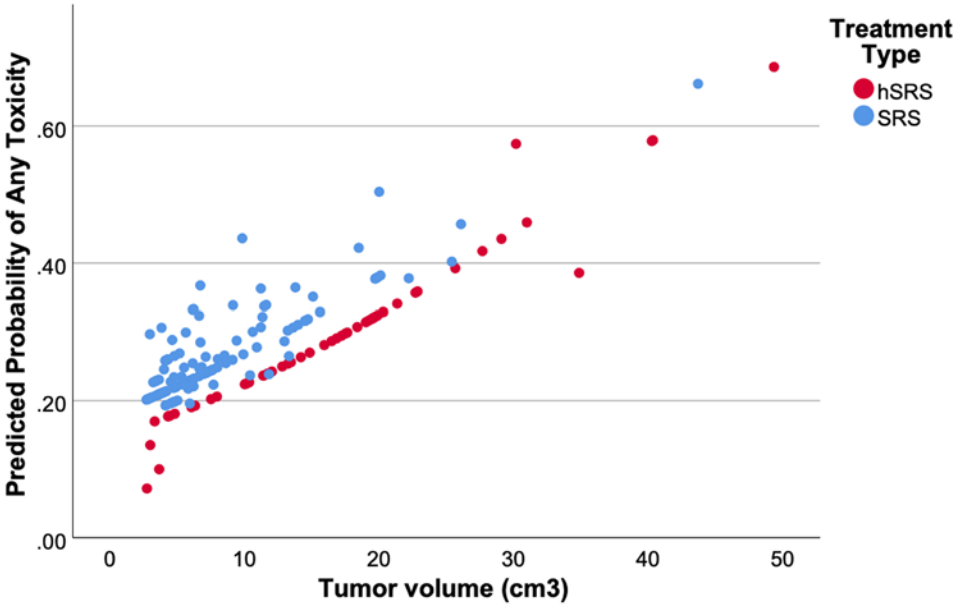

FIG. 3. Graphical representation of individual predicted probabilities of any toxicity by surgery type and meningioma size (p = 0.217). Figure is available in color online only.

as pretreatment edema had no impact on the probability of toxicity. There was no development of radiation-induced malignancy in the patient population.

Discussion

SRS has been a mainstay of treatment for intracranial meningioma for the past 3 decades.[6–8] The major advantages of SRS over surgery include its noninvasiveness, its ability to reach deep-seated tumors[9] or tumors infiltrating major vascular structures, and its ability to safely treat tumors near eloquent brain.[10] In comparison with external-beam radiotherapy (EBRT), SRS is preferable for patients with radiation-induced meningiomas[11] or genetic disorders such as neurofibromatosis type 2, in which there is suboptimal tissue repair.[12,13] Furthermore, SRS induces less cognitive toxicity than EBRT.[14,15] However, potential limitations of SRS include larger lesion size,[16] optic nerve proximity,[17] and higher-grade tumor status.[18] Hypofractionation may help with each of these scenarios by improving the therapeutic ratio over single-fraction SRS.

Hypofractionation is a more recent advancement compared with single-fraction SRS due to the advent of technology that can deliver this treatment. The Gamma Knife has long been a standard treatment platform for the delivery of single-fraction SRS. In the early 2010s, the development of techniques to perform non–frame-based Gamma Knife treatments paved the way for hypofractionation on that treatment platform.[19] In the mid-2000s, the ability to perform large-fraction stereotactic treatments on linear accelerators was developed, and this technology became more ubiquitous in the following decade.[20,21]

Patients with higher-grade meningioma represent a population for which hypofractionation may be potentially helpful. While these tumors may be best treated in the upfront setting with a combination of surgery and EBRT,[22] SRS has an important role in the salvage setting.[23,24] In such cases, these patients have often received a full course of EBRT, and therefore the tolerances of the normal brain tissues need to be considered during treatment planning. Hypofractionation, with its potentially higher therapeutic ratio, may allow for the delivery of a higher biological dose. In the present series, atypical and anaplastic meningiomas had a local control rate of 100% at 1 year.

Several studies have reported on the feasibility and safety of hSRS for the treatment of larger meningiomas. These studies are summarized in Table 2. Unger et al. reported on a series of 173 patients, comparing the rate of posttreatment edema in patients with single-fraction Gamma Knife radiosurgery versus multifraction CyberKnife radiosurgery, and found that single-fraction Gamma Knife had a statistically increased risk of posttreatment edema.[5] Conversely, another series done at the University of Messina assessed 245 meningiomas and was unable to detect a difference in the rate of posttreatment edema between patients with SRS versus hSRS.[25] A third study out of Kaiser Permanente evaluated 30 patients with 38 lesions undergoing treatment of parasagittal or convexity meningiomas with single-fraction SRS (14 patients) or fractionated SRS (16 patients). The authors concluded that patients with larger lesions undergoing fractionation were at decreased risk of posttreatment symptomatic peritumoral edema, which aligns with our results, although their overall cohort and tumor volumes (2.63–7.46 cm^3) were much smaller than ours.[26] Our data show that the risk of posttreatment toxicity increases with tumor size in both the SRS and hSRS groups. However, although the overall radiation doses delivered in the hSRS group were markedly and significantly higher than the radiation doses delivered to comparable sized lesions in the SRS group, there was no statistically significant difference in posttreatment toxicity between the SRS and hSRS groups.

There are several limitations of the present series. Because of the concern for causing posttreatment toxicity with single-fraction SRS, there were relatively few patients with large tumor volumes treated with single-fraction SRS. While we were able to compare the slopes of the toxicity volume relationship between SRS and hSRS, the SRS volumes were limited to those within the confines of the hSRS tumor volumes.

TABLE 2. Prior studies of single-fraction and multifraction SRS for treatment of meningiomas as compared with current cohort

Study	Total No.	Single-Fraction SRS	Multifraction SRS	p Value
Unger et al., 2012[5]				
Pts treated	173	97 (56.1)	76 (43.9)	
Median size, cm^3		4.7	6.6	0.003
Median dose, Gy		15	25	<0.001
Toxicity	13	11 (11.3)	2 (2.6)	0.04
No toxicity	160	86 (88.7)	74 (97.4)	
Conti et al., 2016[25]				
Pts treated	245	NA	NA	
Median size, cm^3		NA	NA	NA
Median dose, Gy		13	54	NA
Toxicity	19	NA	NA	NS
No toxicity	226	NA	NA	
Girvigian et al., 2008[26]				
Pts treated	30	14 (46.7)	16 (53.3)	
Median size, cm^3		2.84	7.46	<0.001
Median dose, Gy		14	50.4 (6 pts), 25 (10 pts)	NS
Toxicity	7	6 (42.9)	1 (6.2)	0.031
No toxicity	23	8 (57.1)	15 (93.8)	
Present study				
Pts treated	172	121 (70.3)	51 (29.7)	
Median size, cm^3		6.1	15.9	<0.001
Median dose, Gy		12	20	<0.001
Toxicity	47	32 (26.4)	15 (29.4)	0.217
No toxicity	125	89 (73.6)	36 (70.6)	

NA = not available; NS = not significant.
Values are given as number of patients (%) unless otherwise indicated. In all groups, an increase in lesion size was associated with an increased risk of posttreatment toxicity. Single versus multifraction treatment showed mixed results in previously published literature.

Conclusions

When controlling for tumor volume, despite higher treatment doses in the hSRS group relative to the SRS group, posttreatment toxicity was not significantly different between the hSRS and SRS groups, and freedom from local failure was improved in the hSRS group. For patients with larger meningiomas, multifraction hSRS may be helpful to limit the risk of posttreatment toxicity, yielding toxicity rates similar to those seen in lower-dose SRS, while maintaining acceptable freedom from local failure.

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Disclosures

Dr. Tatter reported grants from Monteris Medical outside the submitted work. Dr. Chan reported speaker bureau fees from Monteris, DSMB fees from BioMimetix, and advisory board fees from Servier outside the submitted work.

Author Contributions

Conception and design: Tatter, White, Chan, Laxton. Acquisition of data: Smith, Calafiore, Christensen, Munley, Tatter, Chan, Laxton. Analysis and interpretation of data: Smith, Christensen, Kittel, Cramer, Tatter, Chan, Laxton. Drafting the article: Smith, Calafiore, Kittel, Munley, Chan. Critically revising the article: Smith, Calafiore, Christensen, Kittel, Cramer, Tatter, White, Chan, Laxton. Reviewed submitted version of manuscript: Smith, Kittel, Munley, Tatter, White, Chan, Laxton. Approved the final version of the manuscript on behalf of all authors: Smith. Statistical analysis: Kittel. Administrative/technical/material support: Chan.

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