Long-term pain outcomes for recurrent idiopathic trigeminal neuralgia after stereotactic radiosurgery: a prospective comparison of first-time microvascular decompression and repeat stereotactic radiosurgery

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OBJECTIVE Microvascular decompression (MVD) and stereotactic radiosurgery (SRS) are common surgical treatments for trigeminal neuralgia (TN). Many patients who receive SRS have pain recurrence; the ideal second intervention is unknown. The authors directly compared pain outcomes after MVD and repeat SRS in a population of patients in whom SRS failed as their first-line procedure for TN, and they identified predictors of pain control.

METHODS The authors reviewed a prospectively collected database of patients undergoing surgery for TN between 1997 and 2014 at the University of California, San Francisco (UCSF). Standardized data collection focused on preoperative clinical characteristics, surgical characteristics, and postoperative outcomes. Patients with typical type 1, idiopathic TN with ≥ 1 year of follow-up were included.

RESULTS In total, 168 patients underwent SRS as their first procedure. Of these patients, 90 had residual or recurrent pain. Thirty of these patients underwent a second procedure at UCSF and had ≥ 1 year of follow-up; 15 underwent first-time MVD and 15 underwent repeat SRS. Patients undergoing MVD were younger than those receiving repeat SRS and were more likely to receive ≥ 80 Gy during the initial SRS. The average follow-up was 44.9 ± 33.6 months for MVD and 48.3 ± 45.3 months for SRS. All patients achieved complete pain freedom without medication at some point during their follow-up. At last follow-up, 80% of MVD-treated patients and 33.3% of SRS-treated patients had a favorable outcome, defined as Barrow Neurological Institute Pain Intensity scores of I–IIIa ($p < 0.05$). Percentages of patients with favorable outcome at 1 and 5 years were 86% and 75% for the MVD cohort and 73% and 27% for the SRS cohort, respectively ($p < 0.05$). Multivariate Cox proportional hazards analysis demonstrated that performing MVD was statistically significantly associated with favorable outcome (HR 0.12, 95% CI 0.02–0.60, $p < 0.01$). There were no statistically significant predictors of favorable outcome in the MVD cohort; however, the presence of sensory changes after repeat SRS was associated with pain relief ($p < 0.01$).

CONCLUSIONS Patients who received MVD after failed SRS had a longer duration of favorable outcome compared to those who received repeat SRS; however, both modalities are safe and effective. The presence of post-SRS sensory changes was predictive of a favorable pain outcome in the SRS cohort.

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KEYWORDS trigeminal neuralgia; microvascular decompression; stereotactic radiosurgery; long-term pain relief; second procedure

TRIGEMINAL neuralgia (TN) is a facial pain syndrome characterized by sharp, lancinating pain in any of the trigeminal nerve distributions. Microvascular decompression (MVD) and stereotactic radiosurgery (SRS) are among the most commonly performed surgical treatments for TN.

A large body of literature exists describing the efficacy and safety of MVD and SRS for TN; however, significant heterogeneity in patient population and pain type has complicated the interpretation of many studies. First-time and repeat procedures are often included in the same study, and some include patients with atypical pain, especially

ABBREVIATIONS BNI = Barrow Neurological Institute; FIESTA = fast imaging employing steady-state acquisition; MVD = microvascular decompression; SRS = stereotactic radiosurgery; TN = trigeminal neuralgia; UCSF = University of California, San Francisco.

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before the classification for TN was introduced.⁶ In addition, very few studies directly compare outcomes after MVD and SRS, and fewer still use prospectively collected data.

We previously reported our institution's longitudinal experience with MVD and SRS as first-line surgical therapies for medically refractory idiopathic TN;³⁷ however, many patients require a second procedure after initial treatment failure. Pain recurrence rates after initial SRS vary across the literature but range from 40% to 60% over 3–5 years.^{18,22,27,29,30,37} Though previous studies have reported the efficacy of repeat SRS in patients in whom initial SRS has failed, to our knowledge, this is the first comparison of first-time MVD and repeat SRS as the second surgical intervention for residual or recurrent pain after failed first-time SRS. Additionally, we sought to understand the factors that predict favorable outcome after MVD or repeat SRS. Our study hopes to guide clinical decision-making for patients who have continued TN pain after SRS as their index surgical procedure.

Methods

Patient Selection

As we reported previously, data from all patients undergoing surgical evaluation for TN at the University of California, San Francisco (UCSF), was prospectively collected starting in 1997.³⁷ The data in this study include those obtained from patients evaluated between 1997 and 2014. Patients were included only if they met the following inclusion criteria: no evidence of mass lesions compressing the trigeminal nerve, no multiple sclerosis, and had classic type 1 TN pain symptoms. Patients with > 50% constant pain (type 2 TN), those with injury to the trigeminal nerve (neuropathic or deafferentation pain), those with postherpetic neuralgia, and those with atypical facial pain in the setting of somatoform pain disorder were excluded from the analysis.⁶ Patients with < 1 year of follow-up were also excluded from this analysis. In total, 168 patients who met inclusion criteria underwent SRS as the first procedure for medically refractory, idiopathic type 1 TN. Of those, 40 had residual symptoms and 50 developed recurrent symptoms after achieving initial pain freedom. Briefly, residual or recurrent symptoms are defined as having a Barrow Neurological Institute (BNI) Pain Intensity score of IIIb–V at last follow-up. Thirty of the 90 patients in whom first-time SRS failed returned to our institution for a second procedure—15 underwent MVD and 15 underwent repeat SRS—and had at least 1 year of follow-up after this second procedure. All procedures were performed by either N.M.B. or E.F.C. The decision to perform MVD or repeat SRS was based on the patient's request after a discussion of the perceived risks and benefits specific to each patient. This included considerations of the patient's medical comorbidities, any evidence of vascular compression shown on MRI, and patient preference. All research protocols were approved by the UCSF Institutional Review Board (Committee for Human Research).

Data Collection

Data were collected both pre- and postoperatively in

a systematic fashion. At the initial clinic visit, patient demographics, symptom duration, symptom location, symptom features, relevant family and medical history, baseline physical examination findings, and imaging findings were recorded. Postoperative clinic visits were routinely scheduled at 1, 3, 6, and 12 months, and additional visits were scheduled as needed. Phone interviews were conducted to obtain additional follow-up information. Symptom features, medications used, sensory disturbances, and postoperative physical examination findings were recorded. If a patient missed follow-up appointments, information (excluding physical examination findings) was collected via telephone encounters.

Outcome Measures

The primary outcome was BNI Pain Intensity score at last follow-up. The BNI score exists on a scale of I–V as follows: score I, no pain with no medication; score II, occasional pain with no medication; score IIIa, no pain on medication; score IIIb, some pain controlled with medication; score IV, some pain not controlled with medication; and score V, severe pain without relief.³¹ Surgical complications and postoperative sensory changes were recorded as sensory outcomes. Patients were deemed to be pain free if they had no TN pain and were off medications (BNI score I). Patients were deemed to have a favorable outcome if they had BNI scores I–IIIa at last follow-up and had an unfavorable outcome if they had a BNI score of IIIb–V at last follow-up. There were no patients with a score of IIIa in this cohort of patients in whom initial SRS failed.

Procedural Technique

Initial SRS

SRS was performed using a Gamma Knife apparatus. The Leksell stereotactic head frame (Elekta Instruments, AB) was applied after the patients were given a local anesthetic and patients underwent stereotactic MRI. High-resolution T2-weighted images or T2-type fast imaging employing steady-state acquisition (FIESTA) sequences and contrast-enhanced T1-weighted images were used for target planning. The cisternal portion of the trigeminal nerve was targeted with a single isocenter using a 4-mm collimator. Doses for initial SRS ranged from 60 to 85 Gy. Thirteen of 15 patients (86.7%) in the MVD cohort received 80 Gy, with 1 each receiving 60 and 85 Gy. Eight of 15 patients (53.3%) in the SRS cohort received 80 Gy, with 5 receiving 75 Gy and 2 receiving 70 Gy.

MVD

MVD was performed following previously described techniques.^{5,16,23} Briefly, after making a small retrosigmoid craniectomy, the trigeminal nerve was examined for vascular compression at the root entry zone or along its cisternal portion. Compressive arteries or veins were dissected away from the nerve, padded with Teflon felt, and secured with biological adhesive. In 5 cases (33.3%) in which no significant intraoperative vascular compression was visualized, a partial sensory rhizotomy was performed. Intraoperative auditory brainstem evoked potential monitoring was used on all patients.

Repeat SRS

Repeat SRS was performed using the same techniques as initial SRS, except in some cases two isocenters were used. In those cases, one isocenter targeted the cisternal portion of the nerve with shielding from the second isocenter. Doses for repeat SRS ranged from 40 to 80 Gy. Eight patients (53.3%) received 50 Gy, with 2 receiving 40 Gy, and 1 each receiving 45, 55, 60, 70, and 80 Gy.

Postoperative Medication Management

Patients' primary care physicians and neurologists outside the UCSF health system assisted in titration of TN medication postoperatively; therefore, tapers were not standardized. Patients undergoing MVD were typically advised to start weaning their medication 2–6 weeks after becoming pain free, whereas those undergoing SRS were advised to start weaning medications 6 weeks after achieving pain control.

Statistical Analysis

All statistical analyses were performed using JMP Pro version 13.0.0 (SAS Institute Inc.). Continuous predictor and outcome variables were compared using a 2-tailed Student t-test or the Mann-Whitney U-test, as appropriate. Categorical variables were compared with Fisher's exact test. Pain-free duration was plotted using Kaplan-Meier survival analysis, and statistical significance was measured with the log-rank test. Multivariate Cox proportional hazards modeling was used to determine the effect of multiple variables on time to pain recurrence. Only variables with $p < 0.2$ from univariate analysis were used in the multivariate regression model to avoid overfitting. The threshold for significance was set at $p = 0.05$.

Results

Between 1997 and 2015, 168 patients underwent SRS as their initial surgical therapy for medically refractory, idiopathic, type 1 TN and had at least 1 year of follow-up. Ninety patients had an unfavorable outcome (BNI score III–V) at last follow-up. Of those patients, 30 underwent a second procedure at UCSF and had > 1 year of follow-up. Kaplan-Meier survival analysis depicts the time until pain recurrence after initial SRS for these 30 patients (Fig. 1). The median pain-free duration was 13.9 months (IQR 4.1–52.0). The estimated percentages of patients with a favorable outcome after initial SRS were 50% at 1 year and 20% at 5 years. Half of the patients ($n = 15$) underwent first-time MVD as a second procedure, and the remainder underwent repeat SRS. Demographic data for these two cohorts are shown in Table 1. Patients who underwent first-time MVD as the second procedure were younger at the time of their second procedure than those receiving a second-time SRS (mean age 63.3 years vs 75.8 years; $p = 0.04$). Those who underwent MVD were also more likely to receive an initial SRS dose of ≥ 80 Gy than those who underwent repeat SRS (93.3% vs 53.3%; $p = 0.04$). The median initial SRS dose was 80 Gy (IQR 80–80) in the MVD cohort and 80 Gy (IQR 75–80) in the repeat SRS cohort. There were no statistically significant differences in sex, laterality or distribution of pain, family history,

FIG. 1. Pain recurrence after initial SRS for all 30 patients. A Kaplan-Meier survival curve for the entire patient population is shown. Values in the graph represent the number of patients from each group reaching time points indicated by the vertical dashed lines.

symptom duration, age at the time of initial SRS, or time until pain recurrence after initial SRS. Though 2 patients in each cohort had temporary sensory changes after initial SRS, no patients reported numbness, dysesthesias, or anesthesia dolorosa at the time of their second procedure. In addition, though there was a trend for patients in the MVD cohort to have trigeminal nerve compression seen on pre-operative MRI compared to those in the SRS cohort, this was not statistically significant (60% vs 27%, $p = 0.06$). The mean follow-up duration after the second procedure was 44.9 months in the MVD cohort and 48.3 months in the SRS cohort ($p = 0.09$).

Pain Outcomes After MVD or SRS

Patients who underwent MVD as a second-line treatment had a longer pain-free duration than patients who underwent repeat SRS. All patients achieved pain-free status (BNI score I) at some point following their procedure, although the MVD cohort achieved this control faster (4.6 weeks vs 20.1 weeks for the SRS group, $p = 0.05$). At last follow-up, 9 patients in the MVD cohort (60%) and 3 in the SRS cohort (20%) were pain free and off medications (BNI score I). Similarly, 12 MVD patients (80%) and 5 SRS patients (33.3%) had favorable outcomes at last follow-up ($p = 0.03$). One patient in each group (6.7% each) had some pain adequately controlled with medication (BNI score IIb), and 2 patients in the MVD group (13.3%) and 9 in the SRS group (80%) had severe pain without any relief after the second procedure (BNI score V). There were no statistically significant differences in the presence of postoperative sensory changes or adverse event rates between the two cohorts. In addition, there were no cases of painful dysesthesias or anesthesia dolorosa after the second procedure in either cohort. Two adverse events occurred in the MVD group: one patient developed a CSF leak requiring diversion via placement

TABLE 1. Demographic data and clinical characteristics of patients in the MVD and repeat SRS cohorts

Characteristic	MVD	Repeat SRS	p Value
No. of patients	15	15	
Male sex	8 (53.3%)	6 (40%)	0.72
TN laterality			0.43
Right	9 (60%)	12 (80%)	
Left	6 (40%)	3 (20%)	
TN distribution			0.14
V ₁	3 (20%)	4 (26.7%)	
V ₂	0 (0%)	2 (13.3%)	
V ₃	5 (33.3%)	7 (46.7%)	
V ₁ + V ₂	0 (0%)	1 (6.7%)	
V ₂ + V ₃	3 (20%)	1 (6.6%)	
V ₁ –V ₃	4 (26.7%)	0 (0%)	
Family history	0 (0%)	1 (6.7%)	1.00
Mean age at 1st SRS in yrs	60.9 ± 16.1	71.0 ± 14.0	0.08
Mean symptom duration at 1st SRS in mos	95.9 ± 66.1	109.0 ± 87.6	0.65
Dose of 1st SRS			0.04*
≥80 Gy	14 (93.3%)	8 (53.3%)	
<80 Gy	1 (6.7%)	7 (46.7%)	
Transient pain relief w/ 1st SRS	13 (86.7%)	12 (80%)	1.00
Transient sensory change w/ 1st SRS	2 (13.3%)	2 (13.3%)	1.00
Mean time to pain recurrence after 1st SRS in mos	17.9 ± 18.7	38.4 ± 39.7	0.09
Preprocedure sensory disturbance	0 (0%)	0 (0%)	1.00
Mean age at 2nd procedure in yrs	63.3 ± 17.0	75.8 ± 13.9	0.04*
Vascular compression on preop MRI	9 (60%)	4 (26.7%)	0.06
Mean FU in mos	44.9 ± 33.6	48.3 ± 45.3	0.09

FU = follow-up.

Values are presented as the number (%) of patients unless otherwise noted.

Mean values are presented ± SD.

* Denotes statistical significance.

of a lumbar subarachnoid drain followed by wound revision, and the other patient developed unilateral hyperacusis, presumably due to intraoperative injury to the acoustic portion of cranial nerve VIII. These outcomes are summarized in Table 2.

Kaplan-Meier survival analysis was performed to further analyze the difference in pain-free outcomes over time between the two groups. Survival functions depicting time to pain recurrence showed divergent outcomes for the MVD and SRS cohorts. The median duration of favorable outcome was not reached in the MVD group but was 30 months in the SRS group ($p = 0.03$) (Table 2). Percentages of patients with a favorable outcome at 1 and 5 years were 86% and 75% for the MVD cohort compared to 73% and 27% for the SRS cohort, respectively (Fig. 2). Multivariate Cox regression modeling was performed to determine if any other variables could predict pain-free duration. Undergoing MVD as the second procedure was

TABLE 2. Pain relief outcomes among patients in the MVD and repeat SRS cohorts

Outcome	MVD	Repeat SRS	p Value
No. of patients	15	15	
Ever pain free (BNI score I)	15 (100%)	15 (100%)	1.00
Median time to BNI score I in wks (range)	0 (0–56.4)	9.9 (2.3–104.9)	0.001*
BNI Pain Intensity score at last FU			0.04*
I	9 (60%)	3 (20%)	
II	3 (20%)	2 (13.3%)	
IIIa	0 (0%)	0 (0%)	
IIIb	1 (6.7%)	1 (6.7%)	
IV	0 (0%)	0 (0%)	
V	2 (13.3%)	9 (80%)	
Favorable outcome at last FU (BNI score I–IIIa)	12 (80%)	5 (33.3%)	0.03*
Median pain-free duration in mos (IQR)	— (—, —)†	30.0 (7.6, —)†	0.03*
Postop sensory change	4 (26.7%)	6 (40%)	0.70
Complications	2 (13.3%)	0 (0%)	0.48

Values are presented as the number (%) of patients unless otherwise noted.

* Denotes statistical significance.

† These numbers/characters reflect the time it takes for 50% of patients to have pain recurrence after the respective procedure (median), or for 25% or 75% of patients to have pain recurrence (reflected in the IQR). The MVD cohort never reaches 25% failure so all three components cannot be calculated ("—"). The SRS cohort has > 50% but < 75% of patients fail so there is a 25% value and median value (50%) but nothing for the 75% value (upper component of the IQR).

the only statistically significant predictor of favorable outcome (HR 0.12, 95% CI 0.02–0.60; $p = 0.008$) (Table 3). Pain distribution, age at first or second procedure, radiation dose at initial SRS, time to pain recurrence after initial SRS, and time to pain freedom after second procedure were not statistically significant in this multivariate model.

Predictors of Favorable Outcome After MVD

Compression-related characteristics and results of univariate analyses of pain freedom after MVD are reported in Table 4; there were no statistically significant predictors of favorable outcome. Despite the fact that only 60% of MVD patients had MRI evidence of vascular compression on the nerve, intraoperative visualization of compression was seen in 92% of cases. There was a trend for MVD patients with favorable outcome to have arterial compression on the nerve, although this was not statistically significant ($p = 0.07$). Of those patients with evidence of arterial compression, the culprit artery was the superior cerebellar artery in 9 of the 10 cases; the remaining patient had a loop of the anterior inferior cerebellar artery that caused compression. One patient with superior cerebellar artery compression also had dense adhesions around the nerve; in this patient, it was still possible to perform MVD safely. One-third of the patients in the MVD cohort underwent a partial sensory rhizotomy intraoperatively;

FIG. 2. Pain recurrence by procedure type: MVD versus repeat SRS. Kaplan-Meier survival curves for each cohort are shown, with tick marks representing censored events. Values in the graph represent the number of patients from each group reaching time points indicated by the vertical dashed lines.

3 had a favorable outcome and 2 had an unfavorable outcome ($p = 0.24$).

Predictors of Favorable Outcome After SRS

Fifteen patients underwent SRS, and the cumulative SRS dose from the first and second Gamma Knife procedures varied. One patient each received a cumulative radiation dose of 155, 150, and 140 Gy (6.7% each); 6 patients (40%) received 130 Gy; 2 (13.5%) received 125 Gy; 3 (20%) received 120 Gy; and 1 (6.7%) received 110 Gy. There was no significant difference in cumulative SRS dose between those patients with favorable and unfavorable outcomes ($p = 0.71$). In addition, the median time to a pain-free outcome was 14.2 weeks in patients in whom a favorable outcome was achieved, whereas it was 23.1 weeks in those with an unfavorable outcome at the last follow-up ($p = 0.43$). Post-SRS sensory changes occurred in 6 of the 15 patients in the SRS cohort; of these, 5 (83%) had a favorable outcome and 1 (17%) had an unfavorable outcome ($p = 0.002$). No patient developed painful or bothersome dysesthesias. There were no statistically significant associations between favorable outcome and any of the other predictor variables: sex, TN laterality, TN distribution, age at first or second SRS procedure, dose of first SRS, presence of transient pain relief after first SRS, presence of transient sensory change after first SRS, time to pain recurrence after first SRS, and number of isocenters used during the second SRS procedure (Table 5). The median duration of a favorable outcome in patients who did not have post-SRS hypesthesia (defined as decreased sensitivity to touch) was 13 months (IQR 7.6–30), whereas no median pain-free duration was reached in the cohort with sensory changes ($p = 0.01$). Rates of favorable outcome were 83% at 1 and 5 years for those with post-SRS sensory changes compared to 55%

TABLE 3. Multivariate Cox proportional hazard analysis of favorable outcome

Predictor Variable	Hazard Ratio (95% CI)	p Value
Undergoing MVD as 2nd procedure	0.12 (0.02–0.60)	0.008*
Dose ≥ 80 Gy at 1st SRS	0.57 (0.06–4.81)	0.60
TN distribution		0.28
V_1 vs V_1 – V_3	0.49 (0.03–8.23)	
V_2 vs V_1 – V_3	0.02 (0.00–2.46)	
V_3 vs V_1 – V_3	0.23 (0.01–3.97)	
$V_1 + V_2$ vs V_1 – V_3	0 (0–0)	
$V_2 + V_3$ vs V_1 – V_3	0.56 (0.03–11.79)	
Age at 1st SRS	1.54 (0.72–3.63)	0.26
Time to pain recurrence after 1st SRS	1.03 (0.98–1.10)	0.22
Age at 2nd procedure	0.65 (0.27–1.38)	0.27
Time to BNI score I after 2nd procedure	1.03 (0.99–1.07)	0.15

* Denotes statistical significance.

and 0% at 1 and 5 years, respectively, for those without sensory change (Fig. 3).

Discussion

Our study sought to determine the comparative effectiveness of repeat SRS and first-time MVD as the second overall procedure for idiopathic, type 1 TN in patients in whom an initial SRS procedure failed. While MVD has been shown to create long periods of pain freedom,^{3,7,21,34,37} no prior study, to our knowledge, has directly studied the ideal treatment strategy for recurrence after initial SRS. Prior work has shown that radiosurgery alters trigeminal nerve histopathology and that persistent histological changes are likely needed for the effect of radiosurgery to persist.^{1,11,17} Brainstem and trigeminal nerve enhancement is seen after SRS and is associated with pain relief;¹² however, this enhancement takes time to evolve (approximately the median time to pain relief) and is thus not sufficient in and of itself to predict pain freedom. In addition, diffusion tensor imaging tractography in patients who have completed focal radiosurgery demonstrates reduced fractional anisotropy and increased radial diffusivity, suggesting focal changes in myelination after SRS.¹⁴ Despite these microstructural changes to the nerve, patients who receive initial SRS often have residual or recurrent pain. As such, it is unknown if the pathophysiology of TN before treatment is the same as the pathophysiology after initial SRS; similarly, there is reason to believe that the trigeminal nerve has changed after initial SRS, and it is possible that repeat SRS may not be as effective as initial SRS. For this reason, we believe data comparing pain relief outcomes after MVD and repeat SRS are necessary to make clinical decisions in individuals with refractory pain after first-time SRS.

In our cohort of 30 patients who had residual or recurrent pain after first-line SRS for medically refractory TN, MVD led to a significantly longer pain-free period than repeat SRS. The decision to perform MVD as opposed to SRS was not directly influenced by the presence of vas-

TABLE 4. Univariate analysis of MVD outcomes

Variable	Total	Favorable (BNI score I or II)	Unfavorable (BNI score III–V)	p Value
No. of patients	15	12	3	
Male sex	8 (53%)	8 (100%)	0 (0%)	0.08
TN laterality				1.00
Right	9 (60%)	7 (77.8%)	2 (22.2%)	
Left	6 (40%)	5 (83.3%)	1 (16.7%)	
TN distribution				1.00
V ₁	3 (20%)	3 (100%)	0 (0%)	
V ₂	0 (0%)	0 (0%)	0 (0%)	
V ₃	5 (33.3%)	4 (80%)	1 (20%)	
V ₁ + V ₂	0 (0%)	0 (0%)	0 (0%)	
V ₂ + V ₃	3 (20%)	2 (66.7%)	1 (33.3%)	
V ₁ –V ₃	4 (26.7%)	3 (75%)	1 (25%)	
Mean age at 1st SRS in yrs, ± SD	60.9 ± 16.1	60.1 ± 17.5	64.0 ± 10.8	0.64
Symptom duration at 1st SRS in mos, ± SD	95.9 ± 66.1	89.4 ± 64.3	122.0 ± 81.0	0.57
Dose of 1st SRS				1.00
≥80 Gy	14 (93.3%)	11 (78.6%)	3 (21.4%)	
<80 Gy	1 (6.7%)	1 (100%)	0 (0%)	
Transient pain relief w/ 1st SRS	13 (86.7%)	10 (76.9%)	3 (23.1%)	1.00
Transient sensory change w/ 1st SRS	2 (13.3%)	2 (100%)	0 (0%)	1.00
Mean time to pain recurrence after 1st SRS in mos, ± SD	17.9 ± 18.7	17.9 ± 20.2	18.3 ± 14.2	0.97
Mean age at 2nd procedure in yrs, ± SD	63.3 ± 17.0	62.6 ± 18.6	66.0 ± 9.7	0.68
Mean time to pain free in wks, ± SEM	4.6 ± 3.8	4.7 ± 4.7	4.2 ± 2.5	0.93
Rhizotomy performed	5 (33.3%)	3 (60%)	2 (40%)	0.24
MRI compression	9 (60%)	8 (88.9%)	1 (11.1%)	0.53
Intraop compression	14 (91.7%)	11 (78.6%)	3 (21.4%)	1.00
Compressing vessel				0.07
Artery only	10 (66.7%)	9 (90%)	1 (10%)	
Vein only	2 (13.3%)	0 (0%)	2 (100%)	
Artery + vein	2 (13.3%)	2 (100%)	0 (0%)	
None	1 (6.7%)	1 (100%)	0 (0%)	
Sensory change post-MVD	4 (26.7%)	4 (100%)	0 (0%)	0.52

Values are presented as the number of patients (%) unless otherwise noted. Mean values are presented ± SD or ± SEM, as noted.

cular compression on preoperative MRI; there was no statistically significant difference in rates of MRI evidence of compression in the two cohorts. Compared to our previously published analysis of all patients who underwent SRS as their first-line procedure, patients who underwent repeat SRS had a lower median duration of favorable outcome (53 months for initial SRS vs 30 months for repeat SRS).³⁷ Despite differences in patient demographics, including radiation dose at the time of initial SRS, TN distribution, age, and time to pain recurrence after initial SRS, only MVD was a statistically significant predictor of pain relief in the multivariate analysis.

The decision to perform MVD rather than repeat SRS is of particular importance for elderly patients who are more likely to have limiting medical comorbidities. Although MVD can be safe and effective in the elderly,³³ those patients who cannot tolerate general anesthesia should still consider ablative procedures, including radiofrequency lesionectomy and SRS, since SRS in particular has been shown to be very effective in patients older than 70 years of age.⁹ In addition, patients receiving SRS avoid the risk

of postoperative adverse events: Complications of MVD include CSF leak, meningitis, wound infection, facial paralysis, hearing loss, hematoma, and death.⁴ In our study, one MVD patient developed a CSF leak requiring return to the operating room and another MVD patient developed postoperative hyperacusis; no patient who underwent SRS had an adverse event.

Favorable Outcomes After MVD

Univariate analysis in our study failed to uncover any specific predictors of pain freedom in the cohort of patients receiving first-time MVD after failed SRS. Prior reports have suggested that immediate pain relief, male sex, arterial compression, and shorter preoperative symptom duration are predictive of pain freedom after MVD.^{3,24,25,32,36,37} Preoperative MRI demonstrating vascular compression of the trigeminal nerve was present in 66.6% of patients with a favorable outcome and 33.3% of patients with an unfavorable outcome, although this was not statistically significant in our population. This may be due to the small sample size of the study and to the fact that fast spin echo sequences

TABLE 5. Univariate analysis of repeat SRS outcomes

Variable	Total	Favorable (BNI score I or II)	Unfavorable (BNI score III–V)	p Value
No. of patients	15	5	10	—
Male sex	6 (40%)	1 (16.7%)	5 (83.3%)	0.58
TN laterality				0.51
Right	12 (80%)	5 (41.7%)	7 (58.3%)	
Left	3 (20%)	0 (0%)	3 (100%)	
TN distribution				0.28
V ₁	4 (26.7%)	0 (0%)	4 (100%)	
V ₂	2 (13.3%)	1 (50%)	1 (50%)	
V ₃	7 (46.7%)	3 (42.9%)	4 (57.1%)	
V ₁ + V ₂	1 (6.7%)	1 (100%)	0 (0%)	
V ₂ + V ₃	1 (6.6%)	0 (0%)	1 (100%)	
V ₁ –V ₃	0 (0%)	0 (0%)	0 (0%)	
Mean age at 1st SRS in yrs, ± SD	71.0 ± 14.0	72.6 ± 12.9	70.2 ± 15.1	0.76
Mean symptom duration at 1st SRS in mos, ± SD	109.0 ± 87.6	82.4 ± 57.6	122.3 ± 99.4	0.34
Dose of 1st SRS				0.61
≥80 Gy	8 (53.3%)	2 (25%)	6 (75%)	
<80 Gy	7 (46.7%)	3 (42.9%)	4 (57.1%)	
Transient pain relief w/ 1st SRS	12 (80%)	4 (33.3%)	8 (66.7%)	1.00
Transient sensory change w/ 1st SRS	2 (13.3%)	1 (50%)	1 (50%)	1.00
Mean time to pain recurrence after 1st SRS in mos, ± SD	38.4 ± 39.7	45.8 ± 31.9	34.7 ± 44.3	0.59
Mean age at 2nd procedure in yrs, ± SD	75.8 ± 13.9	77.7 ± 12.5	74.8 ± 15.1	0.70
Cumulative SRS dose				0.71
155 Gy	1 (6.7%)	0 (0%)	1 (100%)	
150 Gy	1 (6.7%)	0 (0%)	1 (100%)	
140 Gy	1 (6.7%)	0 (0%)	1 (100%)	
130 Gy	6 (40%)	2 (33.3%)	4 (67.7%)	
125 Gy	2 (13.2%)	2 (100%)	0 (0%)	
120 Gy	3 (20%)	1 (33.3%)	2 (67.7%)	
110 Gy	1 (6.7%)	0 (0%)	1 (100%)	
No. of isocenters w/ 2nd SRS				1.00
1	9 (60%)	3 (33.3%)	6 (67.7%)	
2	6 (40%)	2 (33.3%)	4 (67.7%)	
Mean time to pain free in wks, ± SEM	20.1 ± 6.6	14.2 ± 4.8	23.1 ± 9.7	0.43
Sensory change post-SRS	6 (40%)	5 (83.3%)	1 (16.7%)	0.002*

Values are presented as the number of patients (%) unless otherwise noted. Mean values are presented ± SD or ± SEM, as noted.

* Denotes statistical significance.

such as FIESTA (which are the most likely to demonstrate neurovascular contact) were not routinely obtained in the early years of the reporting period. The degree of agreement between imaging and operative findings with respect to neurovascular contact is promising but does vary in the literature, with Cohen's kappa coefficient ranging from 0.75 to 0.92.^{8,19,20,39} In cases in which no vascular compression was seen intraoperatively, a partial sensory rhizotomy was often performed. Our previous work has shown that although rhizotomy can initially lead to pain relief rates comparable to pure MVD alone, the response rates become divergent at 6 months postoperatively.³⁷ In our cohort of patients undergoing a second procedure, however, there was no statistically significant association between rhizotomy and a favorable outcome; 3 patients (60%; 95% CI 23%–88%) undergoing rhizotomy had a favorable outcome compared to 2 (40%; 95% CI 12%–77%) who had an

unfavorable outcome ($p = 0.24$; Table 4). The discrepancy in outcomes after partial sensory rhizotomy described here may be related to some of the nerve's microstructural changes that occur after initial SRS but may also be confounded by the overall small sample size in this study.

Favorable Outcomes After Repeat SRS

Our analysis is consistent with multiple prior studies that demonstrate that post-SRS sensory changes predict pain freedom after repeat SRS.^{26,29} The only statistically significant predictor of favorable outcome after repeat SRS in our cohort was post-SRS sensory change, which occurred in 100% of patients with a favorable outcome compared to 10% of patients with an unfavorable outcome. The median time to pain recurrence was not reached in the cohort with sensory change but was 13 months in those who did not develop any sensory change.

FIG. 3. Pain recurrence among the SRS cohort by the presence of post-SRS sensory changes. Kaplan-Meier survival curves are shown for each subpopulation, with tick marks representing censored events. Values in the graph represent the number of patients from each group reaching time points indicated by the vertical dashed lines.

Importantly, a majority of patients with permanent post-SRS hypesthesia have described the pain freedom they experience after repeat radiosurgery as worth the sensory changes.²⁶ The major predictor of post-SRS hypesthesia in a prior study was a cumulative radiation dose > 44 Gy to the lateral pons; the cumulative target dose and maximum brainstem dose did not reach statistical significance, however.²⁶ Unfortunately, the optimal radiation dose to the target and to the brainstem has been varied across studies in the literature,^{2,10,15,26,28,35} and it remains controversial whether larger overall radiation doses are predictive of pain freedom after SRS.^{18,22} Some of the variability in cumulative radiation dosing is due in part to differences in study technique, including differences in outcome measures, inclusion of patients with atypical TN features, and follow-up duration. As a result, optimal cumulative target dose ranges from 115 to 150 Gy across the literature. This is similar to the dose range seen in our cohort of patients who received repeat SRS (the cumulative SRS dose ranged from 110 to 155 Gy). Although some patients did receive relatively low doses at the time of repeat SRS, their overall doses were consistent with those reported in the literature. While larger doses of radiation at repeat SRS may have improved pain freedom rates, they could also have caused bothersome dysesthesias or anesthesia dolorosa, which were not experienced by any patient in this series. Besides delivering higher doses of radiation, Wolf and colleagues recently indicated that the ratio of dose to target nerve volume is predictive of pain freedom after SRS.³⁸ Given that post-SRS hypesthesia has been described as the major predictor of pain freedom after repeat SRS in most published reports, future studies should aim to understand how cumulative dose to the lateral brainstem and dose to nerve volume correlate with nerve dysfunction and pain control outcome. Additional reports have suggested that facial numbness after first SRS is predictive of success af-

ter a second SRS procedure;^{13,15} however, we found that all patients in our cohort who had facial sensory dysfunction after their first SRS regained that function prior to their second procedure and that it was not predictive of favorable outcome after repeat SRS.

Conclusions

Multiple surgical interventions exist for medically refractory TN, including the commonly pursued MVD and SRS. Patients often undergo SRS as a first-line therapy; however, residual or recurrent pain is common. In those patients in whom SRS has failed as a first-line surgical procedure, our data suggest that MVD is more likely to lead to a favorable pain outcome than repeat SRS. Still, in those patients in whom MVD carries too high of a risk profile, repeat SRS can lead to pain relief if post-SRS sensory changes are encountered. Although the overall small sample size in this study does limit its ability to be generalized, our data are consistent with the literature for first-time MVD versus SRS,³⁷ and we hope our experience will help counsel physicians and patients on treatment options after initial SRS fails to control their symptoms.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Raygor. Acquisition of data: Raygor, Wang, Ward, Barbaro. Analysis and interpretation of data: Raygor. Drafting the article: Raygor. Critically revising the article: all authors. Reviewed submitted version of manuscript: Chang, Raygor. Statistical analysis: Raygor. Administrative/technical/material support: Ward. Study supervision: Chang.

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