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Project Title: Neurosurgical outcomes for patients with multiple sclerosis related trigeminal neuralgia

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Summary (250 words max single spaced):

Objective:
The aim of this study was to assess the incidence and surgical outcomes of medically refractory multiple sclerosis related trigeminal neuralgia (MS-TN).
Methods:
All Manitobans undergoing first surgery for medically refractory MS-TN between 2000 and 2014 were identified and their charts were reviewed. The outcome measure was the time interval until additional surgery was required, defined as the time to fail (TTF). All surgical outcomes were compared and Kaplan-Meier analysis was applied.
Results:
The incidence of medically refractory MS-TN was 1.2/million/year. Twenty-one patients with 26 surgically treated sides underwent first rhizotomy by GammaKnife (GKRS, 13), glycerol injection (PGR, 10) and balloon compression (BCR, 3). Repeat procedures were required on 23 sides (88%), including GK (24), PGR (19), BCR (25), microvascular decompression (2) and open partial surgical rhizotomy (PSR, 4), with a total of 99 surgeries on 26 sides (range 1-12 each). There were no statistically significant differences in average TTF between first or subsequent GKRS and percutaneous rhizotomies (PGR and BCR), with repeat procedures required in 40%, 60% and 70% at 1, 2, and 3 years respectively. No patients had pain recurrence or required medications after PSR procedure at 4 – 110 months' follow-up. All PSR patients had anticipated facial numbness due to nerve sectioning.
Conclusions:
The minimally invasive rhizotomies for MS-TN were associated with high rates of recurrence and reoperation. Long-term pain relief was best achieved with PSR. Due to the facial numbness after PSR, it may be best utilized as a subsequent procedure rather than an upfront treatment.

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Introduction

The International Headache Society defines trigeminal neuralgia (TN) as electric shock-like pains along the trigeminal nerve distribution that lasts up to two minutes and may be spontaneous or evoked (1). The annual incidence is 4-5/100 000/year (3). The etiology in most cases is compression of the trigeminal root entry zone by blood vessels, usually the superior cerebellar artery (2). A small subgroup, two to four percent, of TN cases is caused by multiple sclerosis (MS) related demyelination of trigeminal nerve projections within the brainstem (3,4).

The initial treatment of TN is the prescription of anti-convulsant medications (e.g. carbamazepine, gabapentin, oxcarbazepine, pregabalin, phenytoin & baclofen), which is titrated to achieve pain control. Dosing is commonly escalated over years as TN pain typically becomes increasingly severe and frequent. If the pain becomes medically intractable or patients develop intolerance to medication side effects, neurosurgery procedures may be considered. Microvascular decompression (MVD) of the trigeminal nerve is potentially curative when TN is caused by neurovascular compression (NVC). Alternatively, or in the absence of neurovascular compression (i.e. MS-TN), a variety of nerve injury procedures may be available including gamma knife rhizotomy (GKRS), percutaneous glycerol rhizotomy (PGR), balloon compression rhizotomy (BCR), radiofrequency rhizotomy, and partial sensory rhizotomy (PSR). These often provide only temporary pain relief but can be repeated if TN pain recurs and again becomes medically refractory.

Sparse literature exists on the effectiveness of neurosurgical treatments for MS-TN patients such that the American Academy of Neurology and the European Federation of Neurological Societies concluded in their guidelines “There is insufficient evidence to support or refute the effectiveness of the surgical management of TN in patients with MS” and recommend that only medically refractory MS-TN patients were suitable for surgery (5). Additionally, no data exists on the actual incidence of medically intractable MS-TN. Thus, the aim of this study was to analyze the utilization and outcomes of surgical procedures for MS-TN in Manitoba.

Methods

Ethics

This study was approved by the University of Manitoba Research Ethics Board (Approval #: HS16272) and the Undergraduate Medical Student Research Committee.

Subjects

All Manitoban patients that underwent surgery for MS-TN at the Winnipeg Centre for Cranial Nerve Disorders (wCCND) between 2001-2014 were identified from a prospectively maintained database.

Data collection

Patient medical charts, consisting of referral letters, consultation notes, imaging reports, operative and follow-up notes were reviewed with relevant information compiled in a database for analysis. All procedures (upfront and retreatments) were recorded for every patient. During follow-ups (clinic visits and telephone interviews), patients were questioned about their TN pain and post-operative complications (numbness, muscle weakness, dysesthesia, infection, etc.)

Surgical Procedures
All surgical candidates had previously failed anti-convulsant medications. The specifics of each operative technique will not be discussed in this report and may be found elsewhere (6,7,8,9,10). As a general treatment philosophy, the choice of surgical modality was considered on the basis of pain severity, urgency for pain relief, pain distribution and patient preference. GKRS provided a slow onset of pain relief over weeks to months and was less effective in pain modulation and discontinuation of medical treatment than percutaneous rhizotomies (PR). GKRS and BCR were utilized to alleviate V1 pain, while PGR was primarily effective to target the V2 and V3 distributions. The anticipated degree of PR induced nerve injury was least with GKRS and greatest with BCR; a more severe injury technique that was generally elected after failure of milder rhizotomies. PSR, an open neurosurgical procedure to partially transect the trigeminal nerve root, was reserved as a “last measure” in this cohort, after multiple failed rhizotomies, due to the associated risks of a craniotomy and consequence of severe sensory loss. Additionally, MVD was selectively utilized in this cohort as NVC was rarely associated with MS-TN.

Outcome Measurement
The primary treatment outcome was time-to-fail (TTF), which is defined as the interval between the surgical intervention and a subsequent procedure. Patients’ specific pain levels were not analyzed in this study. During the interval between procedures (i.e. TTF), patients’ pain levels and medication usage were inconsistent and fluctuated. The indications for repeated procedures were the same as for first surgery: intolerable pain and/or medication related side effects.

Complication Assessment
Due to the longitudinal nature of the study, post-operative complications were only attributed to the previous procedure, if they did not exist pre-operatively. This prevented mistakenly assigning complications to procedures when patients had pre-existing deafferentation pain or sensory symptoms.

Bias
All 99 procedures were performed by study supervisor (A.M.K.) and selection of operation was based upon severity of symptoms, etiology of pain as well as patient and surgeon preferences. To minimize the confounding effect of past procedures on pain modulation, first and subsequent interventions were analyzed separately. Subsequent procedures were analyzed collectively, as there were multiple variations of procedures in order and number.

Statistical Analysis
The Kaplan-Meier method was applied to the TTF data collected on each procedure. Survival curves were generated on Microsoft Excel (Office for Mac 2016). The log-rank test was used for comparisons of TTF between initial GKRS vs PR and upfront vs repeat treatments. A two-sided Student’s t-test was used for comparison where appropriate and P-values of <0.05 were defined as statistically significant.

Results
Twenty-one Manitoba patients, 13 females and 8 males, were surgically treated for their MS-related TN in a 14-year period. Seven patients (4 females and 3 males) were diagnosed with bilateral MS; however, in 2 patients (1 female and 1 male) the symptoms were medically managed on one side. Of the 26 sides that required neurosurgery, 14

were left-sided and 12 were right-sided. At the time of first procedure, pain distribution along the trigeminal nerve was as follows: V1 in 1 patient, V2 in 2 patients, V3 in 6 patients, V2-V3 in 11 patients, V1-V3 in 4 patients, and unknown in 2 patients. At last follow-up, one patient with V1 symptoms developed pain in the V2 and V3 distributions and two patients with V2 and V3 pain progressed to include V1 symptoms. The mean age at TN diagnosis was 53 ± 8 years and the first surgery was performed 4 years later (57 ± 8).

The incidence of medically refractory MS-TN was 1.2 cases/million/year in Manitoba.

In total, 21 MS patients, with 26 medically intractable sides, underwent 99 neurosurgeries for TN, an average of 4.7 procedures/patient (range, 1-16), during a median follow-up time of 59 months (range, 13 months to 158 months).

Of the 26 treated sides, the first procedure breakdown was as follows: 13 GKRS and 13 PR (10 PGR and 3 BCR). Due to the similarity in operative technique and effect on pain modulation, PGR and BCR were analyzed together as PR. The average age at upfront GKRS and PR was 56 ± 8 and 57± 9 years, respectively. Initial pain relief was described in 12/13 (92%) sides that underwent GKRS and 10/13 (77%) sides that underwent percutaneous rhizotomies. As of the last follow-up, two GKRS (13 and 37 month's follow-up time) and one PR (126 month follow-up time) required no repeat treatments. The remaining 88% (23/26 sides) of treatments failed, as patients experienced pain recurrence, required anti-convulsants, and had eventual medication failure (intolerable pain or medication side effects). Additional surgeries were then performed. The average TTF for the first GKRS and PR procedures were 12 ± 8 and 19 ± 17 months, respectively. The difference in TTF between GKRS and PR was not statistically significant. The three treatments that did not require additional surgeries were excluded from TTF calculations.

Additional procedures, 24 GKRS and 43 PR (19 PGR and 24 BCR), were required for the 23 sides that failed upfront surgery. The average TTF for failed repeat GKRS and PR were 17 ± 22 and 13 ± 15 months respectively. The difference of TTF between repeat procedures compared to the initial procedure was not statistically significant.

An additional four patients and five sides with severe recurrent MS-TN pain, despite multiple prior procedures, were scheduled to undergo PSR. In two of these, significant NVC was discovered at surgery leading to a MVD rather than PSR. One patient has had lasting pain relief (80 mo. follow-up time) while the other had recurrent pain and underwent retreatment at 8 months with PSR. There were four PSR procedures that were performed in this cohort and at the last follow-up, all had not required retreatment and all remained pain-free and off medications.

Patients did not suffer from any major surgical complications such as death, stroke or hemorrhage, infection, cerebrospinal fluid leak, or Anesthesia Dolorosa. Persisting procedure-related trigeminal deafferentation pain (dysesthesia) was reported for 8 of 26 sides treated; 4 of the GKRS cases (11%) and 4 of the PR (7%) each. While most of these new dysesthesia developed after multiple procedures, one patient experienced this after their first GKRS. Decreased sensation was reported in 5 GKRS (14%) cases, 14 PR (25%), and all 4 PSR cases (100%). Masseter weakness was reported in 2 GKRS (6%) cases and 4 PR (7%). One patient with medically refractory bilateral pain died of pancreatic cancer.

Discussion

The incidence of MS-TN may be derived from the literature to be 1-2 cases/million/year (3,4). This value seemed to equal the incidence of medically refractory MS-TN we observed in this series. From this data, it may be inferred that nearly all MS-TN patients eventually fail pharmacologic treatment (i.e. suffering from intolerable pain or side effects) and require neurosurgery. This is in keeping with the aggressive nature of MS-TN. Compared to published literature on classical TN, we found MS-TN was diagnosed at a younger age (53 versus 61 years old) (11) and was more commonly bilateral (33% vs. 3%) (12). Also, nearly all MS-TN patients eventually became medically refractory compared to 33 to 50% of classical TN patients (13). Furthermore, medications failed 5 years earlier in the MS-TN cohort and these patients were 13 years younger at the time of first surgery than their classical TN counterparts (14,15,16).

The conventional rhizotomies, GKRS and PR, provided only temporary relief for MS-TN and multiple procedures were necessary for the majority of patients. In contrast, classical TN may be cured with MVD surgery, an option not typically effective for MS-TN. An average of 4.7 procedures per patient were required over a mean follow-up of 59 months. Moreover, the outcome measure of this study, TTF, did not represent a period of effective pain control. Prior to retreatment, all patients had recurrent TN symptoms and had been placed on medications that eventually failed to provide adequate relief. There was a variable period of suffering, between pain recurrence and repeat surgery that was not accounted for in the TTF measure. Prophylactic procedures were not employed before medication failure due to the limited duration of their effectiveness and the risk of post-operative complications including deafferentation pain, which may sometimes be more disturbing than pre-operative TN symptoms. In the series, deafferentation pain was encountered in 8 of 26 sides (31%) usually after multiple procedures.

A comparison of outcomes between GKSR and PR is hindered by differing treatment effects and indications. In patients with intolerable pain requiring immediate relief, PR was preferred to GKRS as the latter often required weeks to months for treatment effect. Therefore, GKRS was generally reserved for patients with up to moderate levels of pain. The effects of this selection bias may have influenced the apparent treatment effectiveness between GKRS and PR, as pre-operative pain levels may have been significantly different. We found that the group with an upfront PR had more than twice as many additional treatments than the upfront GKRS group (52 vs 21). It is unclear whether the difference in number of treatments required for pain modulation between GKRS and PR were related to the difference in aggressiveness of the disease or the difference in total follow-up periods (126 mo. for PR vs 38 mo. for GKRS), rather than treatment modality.

We found that the use of PSR for MS-TN pain was very effective in achieving lasting pain relief; all four patients remained pain free and required no TN medications. No serious complications were encountered, although all patients experienced the anticipated facial numbness as a consequence of partial nerve sectioning. On average, PSR was employed as the 7th procedure (range 4-11) and nearly 8 years after the first surgery. While this period represented a significant period of potential suffering prior to PSR, enthusiasm for earlier utilization of this invasive procedure is balanced against the potential that long term pain relief is sometimes achieved with conventional rhizotomies that usually avoid severe sensory loss. Our data may be interpreted to support earlier use of PSR in patients with recurrent TN after multiple failed surgeries, although not as an upfront treatment. In the future, a multi-center collaboration with a larger sample size could more clearly outline the effectiveness of PSR to treat MS-TN.

Two patients scheduled for PSR were found to have significant NVC intra-operatively, which was not seen on pre-operative imaging. MVD was then performed and provided long lasting pain relief in one patient, indicating a rare case where an MS patient may develop NVC related classical TN. Advanced MRI techniques with sequences, such as CISS and FIESTA, may prove effective in identifying patients with NVC that should be considered for MVD surgery. This has been the practice at our Centre although to date no patient with MS-TN and associated brainstem plaques of demyelination have been found to have concurrent NVC on preoperative diagnostic imaging.

Literature Review
Several MS-TN series have been published on the surgical outcomes for GKRS, PR and PSR. These studies generally analyzed the results of a single type of operation, did not distinguish between first or subsequent treatments, or account for other treatment modalities. Therefore, a direct comparison with our multimodality longitudinal series is subject to several lines of bias and confounding factors. Nevertheless, in order to draw comparisons between these series and our own, we separately analyzed only our patients that underwent GKRS and percutaneous rhizotomies as a first treatment. Patients that underwent PSR were included irrespective of their past procedures as PSR was not performed as an upfront treatment.

The comparison of GKRS series demonstrated our recurrence and retreatment rates of 85% and 92%, respectively, which were higher than other published series (Table 3). Recurrence and retreatment rates were higher among series with longer follow up.

Our initial pain relief rate for PR was comparable to the published data (Table 4); however, our pain recurrence and retreatment rates were higher, 90% and 92% respectively. Compared to the data on GKRS (Table 3), the recurrence and retreatment rate for PR were marginally higher, and PR also had a higher rate of deafferentation complications.

The results of PSR in our study, initial pain relief of 100%, recurrence and retreatment of 0%, were better than other published literature series (Table 5). This may be due to the short follow-up time and small sample size in our series. Generally, the data on PSR described lower pain recurrence and retreatment rate than GKRS and PR.

Strengths and Limitations
Our population-based study encompassed every MS patient in Manitoba that underwent ~~all~~ any form~~s~~ of TN surgery. All of the procedures were performed at the wCCND by the senior author (A.M.K), and long term follow-up was obtained for all patients with reasonable confidence that every procedure underwent was captured in the study.

The study was retrospective and insufficient data was available in some medical charts to assess the outcome measures such as initial pain free response and pain free interval. The study did have a small sample size of only 21 patients with 26 surgically treated sides, resulting in a low statistical power. Moreover, the true incidence and prevalence for MS-TN in Manitoba is not known.

Conclusions

The incidence of medically refractory MS-TN in Manitoba was 1.2/million/year. There was a high failure rate for standard rhizotomies, and multiple retreatments were necessary for symptom relief. Overall, initial surgery for MS-TN failed in 85% after GKRS and 92% after PR. An additional 73 treatments on 23 sides were required over the follow-up period. Conversely, PSR showed 100% ongoing success in pain modulation, although the resultant severe facial numbness limits its usage as an initial treatment. It may be acceptable as an additional treatment following several failed rhizotomies.

Tables and Figures

Table 1. Patient Demographics

No. of Patients	21
Sex	13 F (62%) 8 M (38%)
Bilateral Pain	7 (33%) 2 sides med. Managed
No. of medically refractory sides	26 14 L (54%) 12 R (46%)
Distribution of pain at upfront treatment	V1 = 1 (4%) V2 = 2 (8%) V3 = 6 (23%) V2 and V3 = 11 (42%) V1, V2, and V3 = 4 (15 %) Not specified = 2 (8%)
Distribution of pain at last follow-up	V1 = 0 (0%) V2 = 2 (8%) V3 = 6 (23%) V2 and V3 = 9 (34%) V1, V2, and V3 = 7 (27%) Not specified = 2 (8%)
Mean age at TN Diagnosis	53 ± 8 yo. (range, 39-72)
Mean age at first surgery	57± 8 yo. (range, 44-73)
Mean duration between diagnosis and first surgery	4 ± 4 y (range, 0-15)

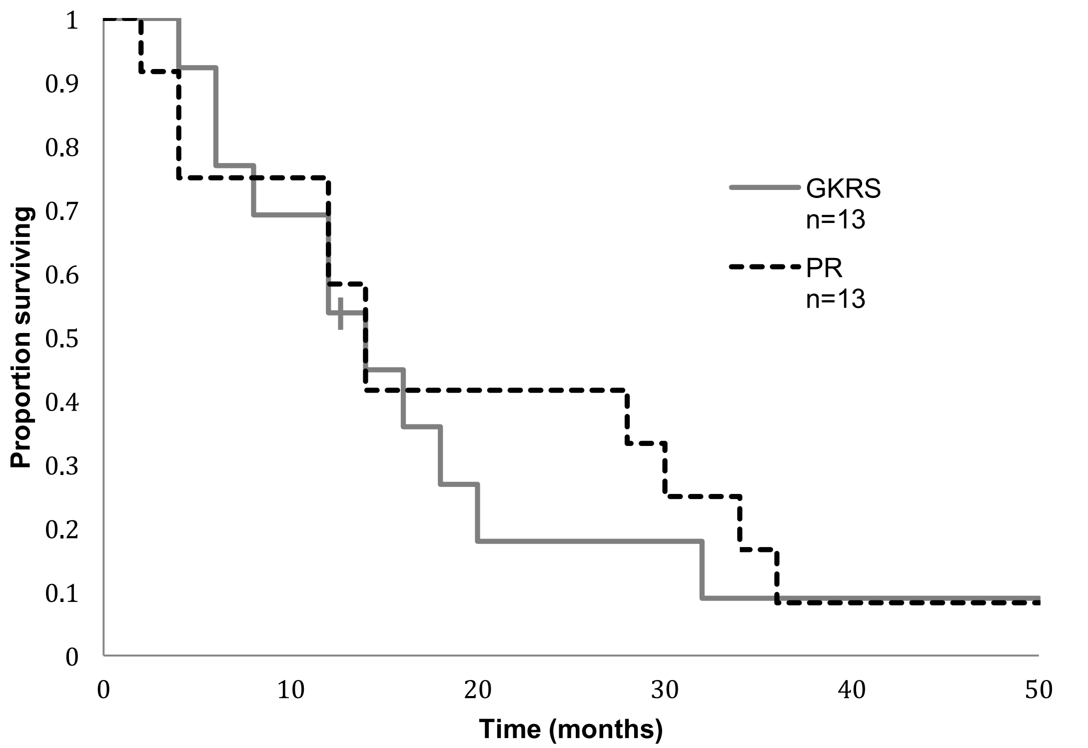

Figure 1. Kaplan-Meier curve of TTF data between upfront GKRS and PR

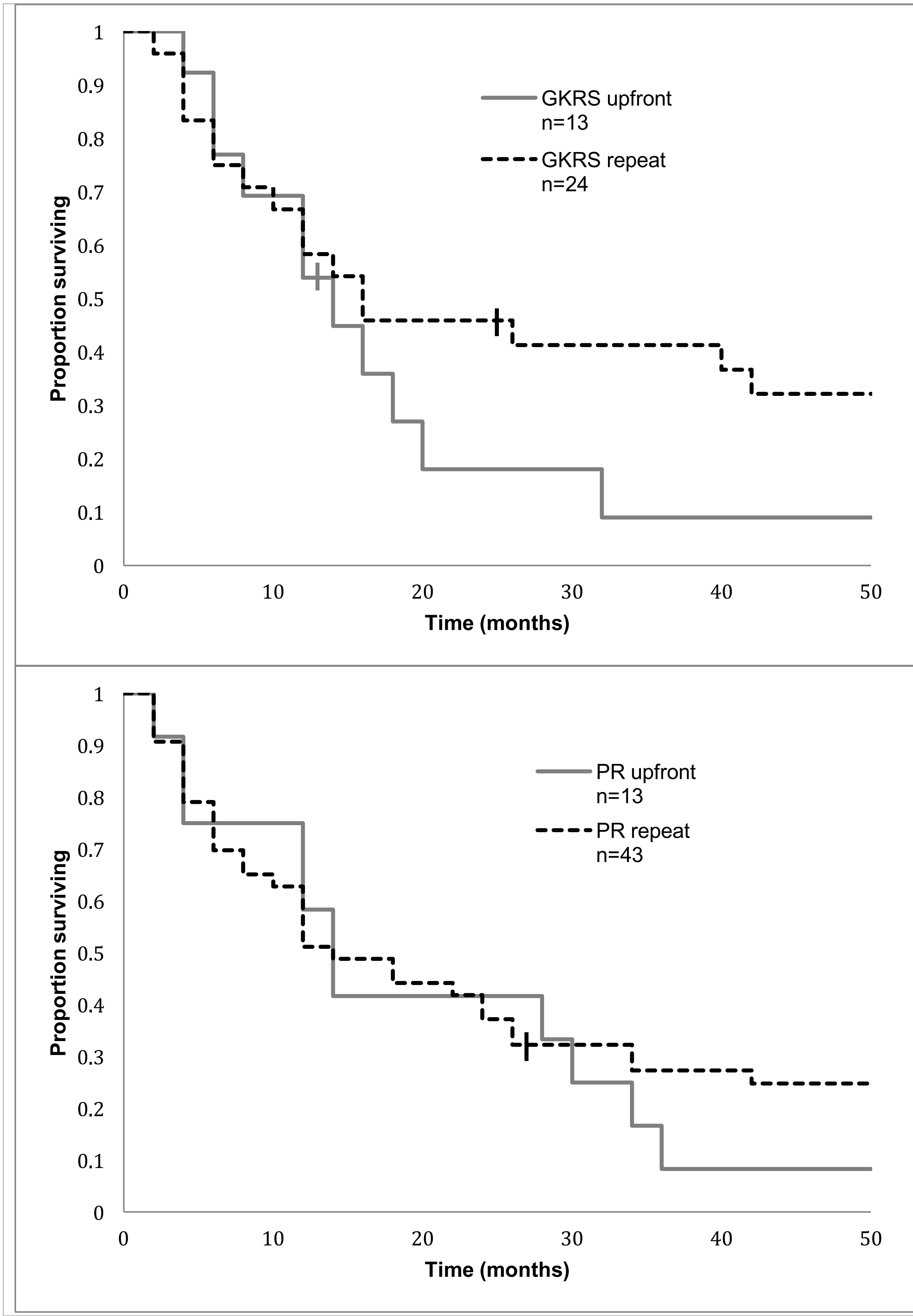

Figure 2. Kaplan Meier curve of TTF data between upfront and repeated procedures

Table 2. Failure rate (%) between GKRS and percutaneous rhizotomies after first and repeat treatment (tx)

Procedure	6 mo.	1 y.	2 y.	3 y.	4 y.
GKRS					
First tx	23	46	82	91	91
Repeat tx	25	42	54	59	68
PGR					
First tx	25	42	58	92	92
Repeat tx	30	49	63	73	75

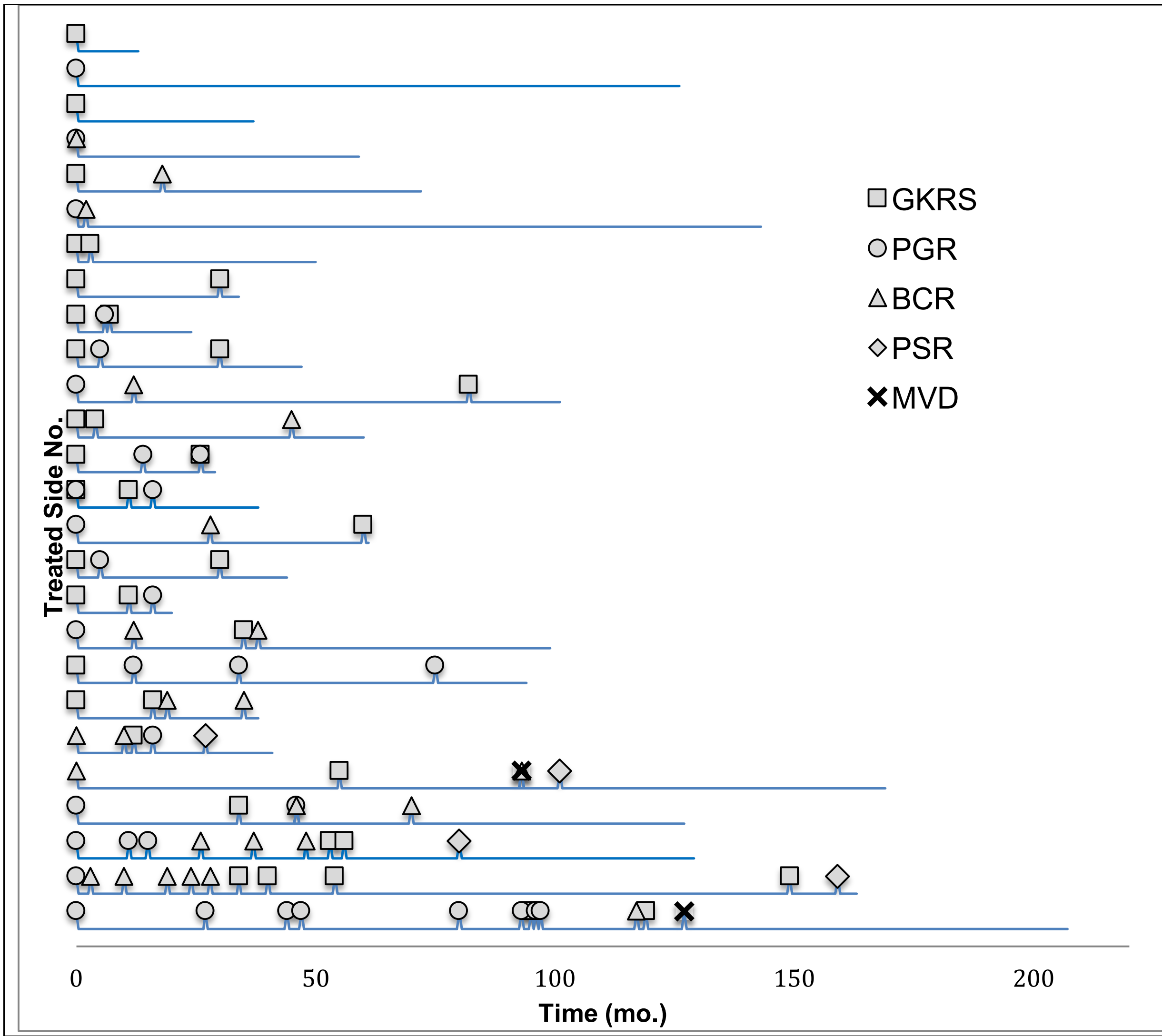

Figure 3. Plot of all patient's sides and treatments underwent. Horizontal lines represent follow-up times.

Table 3. Review of outcomes after GKRS in patients with MS-TN				
Series	Patients	FU time	Results	Complications
Krishnan et al. (2016) *Current series*	12 (13 sides)	38 mo. (median)	Initial pain relief: 12/13 (92%) Pain recurrence: 10/12 (83%) Retreatment: 11/13 (85%) No. additional procedures: 21	Decreased sensation in 2/13 (15%) Deafferentation pain in 1/13 (8%)
Tuleasca et al. (2014) (21)	43	54 mo. (median)	Initial pain relief: 39/43 (91%) Pain recurrence:24/39 (62%) Retreatment: 22/43 (51%) No. additional procedures: >38	Sensory dysfunction in 4/43 (9%)
Mohammad-Mohammadi et al. (2013) (20)	24 (first treatment only)	69 mo. (median)	Initial pain relief: 12/24 (50%) Pain recurrence: 8/12 (67%) Retreatment: NS No. additional procedures: NS	None
Mathieu et al. (2012) (19)	27	39 mo. (median)	Initial pain relief: 24/27 (89%) Pain recurrence: 11/24 (46%) Retreatment: 12/27 (44%) No. additional procedures: 12	Numbness in 6/27 (22%)
Zorro et al. (2009) (18)	37	57 mo. (median)	Initial pain relief: 36/37 (97%) Pain recurrence: 14/36 (39%) Retreatment: 15/37 (41%) No. additional procedures: 15	Paresthesia in 2/37 (5%)
Rogers et al. (2002) (17)	15	17 mo. (mean)	Initial pain relief: 12/15 (80%) Pain recurrence: NS Retreatment: 5/15 (33%) No. additional procedures: 5	Numbness in 2/15 (13%)

Table 4. Review of outcomes after PR in patients with MS-TN				
Series	Patients	FU time	Results	Complications
Krishnan et al. (2016) PGR & BCR *Current series*	9 (13 sides)	126 mo. (median)	Initial pain relief: 10/13 (77%) Pain recurrence: 9/10 (90%) Retreatment: 12/13 (92%) No. additional procedures: 52	Decreased sensation in 4/13 (31%) Deafferentation pain in 1/13 (8%)
Martin et al. (2015) BCR (24)	17	43 mo. (mean)	Initial Pain relief: 14/17 (82%) Pain recurrence: 12/14 (86%) Retreatment: 12/17 (70%) No. additional procedures: 26	Post-op complications in 9/43 (21%) incl. meningitis, dysesthesia, cheek hematoma, masseter weakness
Mohammad-Mohammadi et al. (2013) (20) PGR & BCR	58 (first treatment only)	69 mo. (median)	Initial Pain relief: 47/58 (81%) Pain recurrence: 31/47 (66%) Retreatment: NS No. additional procedures: NS	Temporary numbness in 14/58 (24%) and severe numbness and impaired corneal reflex in 2/58 (3%).
Montano et al. (2012) BCR (23)	21	52 mo. (mean)	Initial Pain relief: 17/21 (81%) Pain recurrence: 8/17 (47%) Retreatment: 12/21 (57%) No. additional procedures: 15	Hypoesthesia in 2/21 (10%)
Mallory et al. (2012) PGR & BCR (22)	136	13 mo. (median)	Initial Pain relief: 90/136 (67%) Pain recurrence: 65/90 (72%) Retreatment: 80/136 (60%) No. additional procedures: NS	Numbness in 72/136 (53%), other complications in 14/136 (10%) incl. thalamic hemorrhage anesthesia dolorosa. corneal anesthesia, Horner syndrome, diplopia, dysesthesia,

Mathieu et al. (2012) PGR (19)	18	38 mo. (median)	Initial Pain relief: 18/18 (100%) Pain recurrence: 7/18 (39%) Retreatment: 6/18 (33%) No. additional procedures: 6	Meningitis in 1/18 (6%), Numbness in 11/18 (61%)

Table 5. Review of outcomes for PSR in patients with MS-TN				
Series	Patients	FU time	Results	Complications
Krishnan et al. (2016) *Current series*	3 (4 sides)	33 mo. (mean)	Initial Pain relief: 4/4 (100%) Pain recurrence: 0/4 (0%) Retreatment: 0/8 (13%) No. additional procedures: 0	Numbness in 4/4 (100%)
Abinav et al. (2012) (26)	23	33 mo. (mean)	Pain relief at 3 months: 20/23 (87%) Pain recurrence: 3/20 (15%) Retreatment: NS No. additional procedures: NS	Facial numbness in 22 (95%)
Branislav et al. (2009) (25)	8	108 mo. (mean)	Initial Pain relief: 8/8 (100%) Pain recurrence: 3/8 (37%) Retreatment: 1/8 (13%) No. additional procedures: 1	Dysesthesia in 2/8 (25%), CSF rhinorrhea in 1/8 (13%)

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