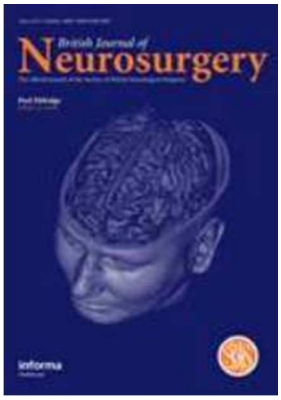

Long-term pain relief at five years after medical, repeat surgical procedures or no management for recurrence of trigeminal neuralgia after microvascular decompression: analysis of a historical cohort

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Long-term pain relief at five years after medical, repeat surgical procedures or no management for recurrence of trigeminal neuralgia after microvascular decompression: analysis of a historical cohort

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ABSTRACT

Background: Management strategies for the recurrence of trigeminal neuralgia after microvascular decompression include repeat procedures, medical management or no further therapy. No consensus exists as to which strategy is best for pain relief. The aim of this study was to determine the characteristics of patients with recurrences after microvascular decompression in the cohort, and to compare long-term pain relief between different management strategies.

Materials and methods: A historical cohort of patients who underwent microvascular decompression at a neurosurgical institution between 1982-2002, followed up by postal survey at five years, was included. Characteristics of patients who experienced a recurrence were compared to those who were recurrence free, and pain relief was compared between each management strategy.

Results: From 169 responders who were included in the study, 28 (16.6%) experienced a recurrence after MVD. No characteristics were significantly different between patients who experienced a recurrence and those who did not. Repeat procedures, including repeat microvascular decompression, partial sensory rhizotomy or radiofrequency thermocoagulation, yielded the highest proportion of pain relief after recurrence (p = 0.031), with 63.6% of patients pain-free at five-years. There was no evidence to suggest that the choice of repeat procedure influenced the likelihood of pain relief after recurrence. No further treatment yielded 57.1% pain-free, whereas medical therapy had the lowest proportion of pain free patients, at 10.0%.

Conclusion: A variety of options are available to patients for recurrence of TN after microvascular decompression with repeat procedures yielding the greatest likelihood of long-term pain relief in this historical cohort. The choice of management should consider the mechanism of recurrence, the benefits and risks of each option and the severity of the pain. Regardless of the management strategy selected, careful phenotyping of patients before and after surgery is paramount.

INTRODUCTION

Microvascular decompression (MVD) is the most common neurosurgical approach for classical trigeminal neuralgia (TN) with neurovascular compression (NVC). MVD has a risk of mortality below 0.3%, and above 80% of patients remain pain-free without need for further treatment.[1,2] Within the first four post-operative years, MVD provides the best results of all procedures, whilst reducing the risk of complications that come with ablative procedures.[3] These, in addition to its safety in elderly patients,[4] make MVD an attractive option for the definitive treatment of TN.

A proportion of patients with TN experience recurrence of their pain after the procedure. Approximately 4% of patients per year experience recurrence of TN after MVD, dropping to 1-2% per year by the sixth year after surgery.[5] Over a period of 10-20 years, the recurrence rate of TN after MVD may exceed 10%.[3] Recurrence after MVD is caused by new or additional NVC, formation of arachnoid adhesions or granuloma and slippage of padding. [6-9] Though the proportion of patients experiencing recurrence is considerable, there is no consensus as to its optimal management. Repeat procedures may include invasive options such as repeat MVD and partial sensory rhizotomy (PSR), or percutaneous options such as radiofrequency thermocoagulation (RFT and glycerol injection (GI) which are less invasive . Some patients opt out of further treatment, or choose medical therapy alone. A few small cohort studies compare outcomes between the different management strategies after a recurrence, [9-13] but a comparison of different surgical interventions, including invasive or percutaneous procedures, against medical therapy and no further treatment is required. This complicates the decision process for patients and clinicians when deciding between different treatments.[14]

Our team has access to a historical database, prospectively maintained and gathered from one neurosurgeon's entire posterior fossa surgical practice between 1982 and 2002. This database has been previously reported in terms of patient satisfaction and post-operative quality of life.[15,16] A systematic assessment of recurrences after MVD in this cohort would both add to the paucity of literature comparing treatment options after recurrence, and inform future reports as to whether repeat procedures, medical management or no therapy at all is best.

Aims and hypothesis

The aim of this study was to define the characteristics and determine management and pain outcome of patients with a recurrence after first MVD in our cohort. We hypothesize that patients who experience a recurrence after MVD will have distinguishable characteristics pre-operatively, and that repeat operations, including invasive or percutaneous procedures, will provide better pain relief than medical management or no therapy.

METHODS

Participants and eligibility

Ethical approval was given by Frenchay Hospital Bristol LREC (Project Number: 2001/60). Patients were drawn from one neurosurgeon's entire posterior fossa surgery practice from 1982 – 2002, reported in terms of satisfaction, quality of life and used to validate and design a patient-experience assessment set.[15,17] All patients who underwent MVD for primary idiopathic TN, diagnosed using the second iteration of the International Classification for Headache Disorders, were included.[18] Patients were excluded: with a secondary cause of trigeminal neuralgia including malignancy or multiple sclerosis, with a concurrent cranial nerve disorder, or with a failure of their MVD. Failure was defined as incomplete pain relief after MVD, requiring medication to obtain pain relief or surgery within 3 months after initial operation. Patients who had undergone prior procedures for TN were separated from the cohort and analysed independently.

Data collection

Patients were followed up by postal survey at a mean of five years postoperatively (with a standard deviation of 3.8), using a comprehensive assessment set for patient experience and postoperative complications.[17] Prior to that they had annually completed a short one page questionnaire returned to the department. Responses were returned to the independent observers including one physician and one neurosurgeon. Recurrence of TN was defined as any post-operative pain at least three months after MVD. Recurrence was classified as major (severe pain requiring drugs or repeat procedures) or minor (transient, mild pain, resolving within 1-2 months). Characteristics extracted from healthcare records include: previous procedures, age at operation and onset of TN, gender, duration of symptoms, division of trigeminal nerve involved, side of pain, operative findings and whether compression was arterial, venous or mixed, postoperative pain relief, presence of and time to recurrence and second treatment. The management strategy for recurrence was also collected from the assessment set, including repeat procedures (invasive procedures such as MVD or PSR and percutaneous procedures such as RFT or GI), medical management (patients taking drugs licensed for TN) or no management (opting for natural remission with no further procedures or medication). The outcomes, as determine by the assessment set, was whether the patient was pain free or not, taking drugs for control of TN and the frequency of drug use at the time of follow-up. Data was anonymised and entered on a spreadsheet.

Data analysis

Comparison of the characteristics between patients with a recurrence and those without were performed using Mann-Whitney *U* and χ^2 tests. Contingency analyses to compare outcomes between management strategies after recurrence were performed using a χ^2 test, or Fisher's exact test where cells had a value less than 5. All data were managed and statistics performed using IBM SPSS Statistics for Macintosh Version 24.0 (IBM

Corp., Armond, NY). All continuous variables were found to have a skewed distribution, and median values are reported with interquartile ranges (IQR). *p* values less than or equal to 0.05 were considered statistically significant. Graphs were drawn using Prism for Macintosh, Version 7 (GraphPad Software Inc., San Diego, CA).

RESULTS

Study participants and characteristics

From 1982 to 2002, 284 patients underwent MVD for TN at the neurosurgical centre and were sent assessment sets at a mean follow-up of five-years **(Fig. 1).** From these, 64 (22.5%) were excluded due to: death, non-response, lack of postal address or telephone-follow up only. From the remaining 220 patients who responded to the survey, 18 (8.2%) were excluded due to failure of MVD. 33 (15.0%) responders had previous procedures for relief of TN, and were separated from the cohort and analysed independently. For the main analysis, this left 169 (59.5%) patients for inclusion from the original MVD cohort.

Twenty eight (16.6%) patients experienced a recurrence of their TN within the five-year period after MVD, including 18 major recurrences and 10 minor recurrences. The characteristics of patients with a recurrence after MVD were compared with those who were recurrence free **(Table 1).** Some variables had missing data. Categorical data with missing variables are denoted with denominators. Continuous variables with missing data included age of onset of symptoms (recurrence, n = 4; recurrence-free, n = 34) and duration of symptoms (recurrence, n = 4; recurrence-free, n = 36). No characteristics were significantly different between patients with a recurrence after MVD and those recurrence-free. The median time to recurrence was 15.7 months (IQR; 8.0-44.2), with 52.0% of these occurring within the first 18 months postoperatively. In all patients, arterial compression was the most common surgical finding, and this did not differ whether the patient experienced a recurrence or not. Details of the vascular findings at operation in patients are provided in **Supplementary Table 1**. The 64 non-responding patients had a significantly higher age at diagnosis (U = 6280.0; p = 0.019) and consequently at surgery (U = 8243.0; p = 0.032) compared to 220 who responded.

Management strategies and pain relief at five years for recurrence after MVD

At a mean five year follow up, the choices that patients made for treatment of recurrence and their effect upon pain relief were compared. From 18 patients with a severe recurrence, four (22.2%) opted for no further treatment, four (22.2%) opted for medical management alone and 10 (55.6%) opted for repeat procedures, including three MVDs, three PSRs and four RFTs. From the 10 patients with a minor recurrence, three (30.0%) opted for no further treatment, six (60.0%) opted for medical management and one (10.0%) opted for an RFT. By the end of the five-year follow up period, 12 out of 28 (42.9%) patients with a recurrence were pain-free. Seven (25.0%) were using medication for control of pain, of

which five (17.9%) were using medication once daily and two (7.1%) used medication twice or more per day. The severity of recurrence did influence the likelihood of being pain-free or requiring drugs to control pain at five years.

The difference in proportion of patients who were pain-free between no treatment, medical therapy and further procedures varied significantly ($\chi^2 = 6.9$, $p = 0.031$; **Fig. 2).** Repeat procedures yielded the highest proportion of pain-free patients (7/11; 63.6%), including repeat MVD (2/3; 66.7%), PSR (2/3; 66.7%) or RFT (3/5; 60.0%). After repeat procedures, no further treatment yielded the next highest proportion of pain-free patients (4/7; 57.1%), whereas medical therapy had the lowest proportion (1/10; 10.0%). The proportion of patients using medication to relieve pain at five-year follow up did not vary significantly between no treatment, medical therapy or repeat procedures ($\chi^2 = 2.8$, $p = 0.25$). The frequency of drug use also did not vary significantly between these groups ($\chi^2 = 5.8$, $p = 0.21$). The outcomes for patients with failure of MVD are provided in **Supplementary Fig. 1)**.

Outcomes in patients with prior procedures for TN

Of the 33 patients with procedures for TN prior to MVD, from which 16 were peripheral surgery (cryosurgery or neurectomy of peripheral branches) and 17 were performed at the Gasserion ganglion level, 11 (33.3%) experienced a recurrence after the subsequent MVD, including 4 with peripheral surgery and 7 at the Gasserion ganglion level. This was a significantly higher proportion than the 28 out of 169 patients without prior procedures who experienced a recurrence after MVD ($\chi^2 = 5.0$, odds ratio; 2.5, 95% CI; 1.1-3.5, $p = 0.026$). Eight of the 11 recurrences in patients with prior procedures were major, and three were minor. There were no significant differences in characteristics between the study cohort and those who had prior surgery. Only two out of the 11 patients who had prior surgery experienced a recurrence were pain-free at five-year follow-up **(Supplementary Fig. 2)**. Patients with a recurrence after MVD who had undergone prior surgery required an increased frequency of drug use for pain relief (OR = 6.0; 95% CI, 1.2-29.7; Fisher's exact test; $p = 0.041$), compared to those who had a recurrence after MVD as their first procedure. There were no significant differences in pain relief between the different treatment options for patients who experienced a recurrence with prior surgery.

DISCUSSION

In this analysis of recurrences after MVD in our historical cohort, no clear characteristics distinguished patients who experience a recurrence of TN after MVD within five years. Patients who experience a recurrence opt for a variety of strategies including medical therapy, repeat procedures or no therapy at all. Repeat procedures, including MVD, PSR or RFT, yielded the best pain relief, followed by no further treatment, with medical management as the worst option for pain relief. There was no evidence to suggest that the choice of procedure influenced the likelihood pain relief. Patients with a prior procedure had poorer pain relief, and the various management strategies did little to change this. This may have been due to addition nerve injury from the procedure itself.

To our knowledge, this is the first study to compare different surgical options to medical management or no therapy for the treatment of recurrence after MVD. Though the database is historical, it was prospectively maintained, meaning that even those with failed MVD, who were excluded from final analyses, were followed-up at five years. This study is not without limitations. The rarity of TN,[3] in addition to the 16.6% of patients who experienced a recurrence in this study, resulted in a small sample size, which limits the interpretability of contingency analyses, prohibits the use of a regression model to determine predictors of recurrence and prevents a thorough comparison between invasive procedures, such as PSR or MVD, with percutaneous procedures such as PSR. The older criteria used for diagnosis in this study have been superseded by more contemporary ones, which differentiate TN into different subtypes.[19,20] As different subtypes of TN, which may not have been picked up by the study, have different responses to surgery,[21-24] this may confound analyses. The degree of vascular compression may be a major prognostic factor for pain outcomes.[21] At the time of posterior fossa procedures in these patients, intraoperative detail such as the degree of distortion on the trigeminal nerve and its effect on the nerve's appearance were not appreciated, and so were not available for this study. Non-responders had a significantly greater age at diagnosis and surgery compared to the cohort, predominantly due to death or no answer to postal survey, meaning that outcomes of some of the older population may have been missed.

Female gender, duration of TN greater than 8 years, memorable onset, venous compression and lack of immediate pain relief have been associated with recurrence of TN after surgery.[11,21-26] However, in agreement with one study, we found no such characteristics that defined patients with a recurrence.[21] Compression can occur at multiple sites but the exact location of the compression may be an important factor in determining recurrence. It has been postulated that the anatomical location of transition between central and peripheral myelinated fibres, termed the root entry zone (REZ), may be at risk of compression by pulsatile vessels. Two

prospective observational studies have demonstrated that patients with significant atrophy and compression of the REZ, as noted on MRI are likely to benefit the most from MVD.[27,28] High quality MRI were not available at the time this study was done and so the precise location of the compression cannot be confirmed. This may account for the findings from this study that the predominant vessels causing NVC are arterial, but that higher recurrences were not found in those with venous compression, as previously suggested by others who, at the time, may not have had access to high quality MRIs.[5,24] There appears to be consensus that a repeat MVD is a viable option for patients with a recurrence, albeit pain relief and numbness are significantly worse for repeat compared to primary MVD.[6,8,29,30] Other studies of repeat procedures after recurrence have shown good results for partial nerve sectioning, rhizotomy and stereotactic radiosurgery.[9,10,13] These operations yield better pain relief after MVD than after other destructive procedures,[13] so the type of prior procedures in patients is an important factor to consider. Tyler-Kabara and colleagues found that prior destructive procedures were a negative predictor for short-term, but not long-term pain relief postoperatively,[23] with Rath and colleagues also showing poor outcomes for repeat destructive procedures.[11]

Medical management of recurrences was worse for pain relief when compared to repeat procedures. A case series following up 80 patients treated with MVD found, that in five patients with major recurrence of TN, none were amenable to medical management.[12] The discontinuation of therapy was shown to yield satisfactory outcomes, and to our knowledge this is the first time that no therapy has been shown to be nearly as efficacious as repeat procedures for management of a recurrence. Some patients may opt for no medical therapy as the side effects of the medications may outweigh their benefit. Conversely some who have had a recurrence may be reluctant to stop all medication in case of a more severe recurrence.

The disparity in predictors for recurrence of TN after MVD may be due to different phenotypes of TN within a study population. Burchiel and colleagues have advocated dividing patients into type 1 and type 2, with the latter having a prolonged background pain for more than half of the time.[31] It is hypothesised that patients with TN type 2 may have a higher recurrence rate. Reports using this classification show poorer outcomes for TN type 2 after MVD or stereotactic radiosurgery.[22,32,33] However, Sindou and colleagues found no difference in outcomes after surgery between classical TN and TN with a baseline of permanent pain, which they defined as atypical TN.[32] It is proposed that the mechanism of continuous pain observed in TN phenotypes in these studies may differ from the paroxysmal pain of TN,[20] underlying the variable response to surgery and the heterogeneity of predictors for recurrence. It is thus essential to carefully phenotype all patients with TN, both clinically and using high quality imaging whose sensitivity and specificity is improving,[35] and to use the most contemporary diagnostic criteria such that studies are comparable and data reproducible.[19]

When choosing treatment options after MVD, three factors should be taken into consideration. Firstly, the mechanism of return to pain may guide treatment. The failure of medical management indicates a mechanical

fault that may not be amenable to contemporary pharmacological therapies. The mechanism of recurrence may be deduced by intraoperative findings and imaging, to guide choice of repeat procedure. For example, in the absence of NVC, Ishikawa and colleagues propose that arachnoid thickening can lead to distortion between the root and surrounding structures.[36] Sindou and colleagues found that focal arachnoiditis results in poorer outcomes. These arachnoid changes could result movement and hyper-excitability of the nerve. As such, Revuelta-Gutierrez and colleagues suggest that all the arachnoid is freed, and mild neuropraxia induced by compressing bipolar tips at the root entry zone.[37] However, when NVC is found, a repeat MVD may be more appropriate. The second factor to be taken into consideration when choosing treatment options is the additional complications that may arise. For example, the sensory loss associated with destructive procedures is common,[36,37] and its impact on quality of life can be significant and should be communicated to patients.[16,38,39] Thirdly and finally, the severity of recurrence should be determined by the patient, considering the option of no treatment at all, which may result in good pain relief in the long-term whilst also avoiding the complications and risks associated with neurosurgery. Whether repeat procedures, medical management or no treatment is chosen, the management for a recurrence after MVD should take into consideration risks and benefits of each option. These should be made clear to the patient to ensure informed consent and a shared-decision making process.

Conclusion

Recurrence after MVD is a common issue that is difficult to manage, though its predictors are unclear. There are a variety of options for the management of a recurrence, including repeat procedures, medical or no treatment. Our study indicates that repeat procedures, including repeat MVD, PSR or RFT yield the greatest likelihood of pain relief, and medical management the worst. Those who experience a recurrence after previous procedures had poor outcomes in this cohort. Ultimately, the decision-making process for a recurrence after MVD requires careful phenotyping before and after surgery, consideration of the mechanism of recurrence and balance of the benefits and risks of each treatment strategy.

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Declaration of interest: The authors have no known conflicts of interest to declare. Both authors contributed to the design of the study. JZ designed and distributed the assessment set and organised its data entry. DJ analysed the data and wrote the first draft. All authors contributed equally to the subsequent revision and

acceptance of the final manuscript, and are accountable for all aspects of the study.

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APPENDIX

Supplementary Table 1 | Vascular findings at MVD for patients with and without recurrence

Operative finding	Recurrence group (n = 26)	Recurrence free group (n = 141)
SCA (%)	12 (52.2)	78 (64.5)
AICA (%)	5 (21.7)	29 (24.0)
Basilar artery (%)	1 (4.3)	0 (0.0)
Petrosal artery (%)	1 (4.3)	2 (1.7)
Unknown artery (%)	0 (0.0)	1 (0.8)
Mesencephalic vein (%)	1 (4.3)	3 (2.5)
Trigeminal vein (%)	1 (4.3)	3 (2.5)
Unknown vein (%)	0 (0.0)	3 (2.5)
Multiple veins (%)	1 (4.3)	2 (1.7)

AICA, anterior inferior cerebellar arterior; SCA, superior cerebellar artery

TABLES

Table 1 | Characteristics of patients with and without recurrence five years after MVD

Characteristic	**Recurrence group (n = 28)**	**Recurrence free group (n = 141)**	**Test; *p* value**
Median age in years (IQR)	59.0 (46.3-70.8)	60.0 (51.0-69.0)	$U = 1843.0$; ns
Gender: female (%)	18 (64.3)	80 (56.7)	$\chi^2 = 0.5$; ns
Median age at onset (IQR)	49.5 (41.3-65.8)	54.0 (45.0-62.0)	$U = 1158.0$; ns
Median duration of symptoms in years (IQR)	5.0 (2.0-7.0)	5.0 (3.0-8.0)	$U = 1168.5$; ns
Division (%)			$\chi^2 = 7.9$; ns
V1	*1 (3.6)*	*7/124 (5.6)*	
V2	*2 (7.1)*	*17/124 (13.7)*	
V3	*6 (21.4)*	*26/124 (21.0)*	
V1 + V2	*2 (7.1)*	*23/124 (18.5)*	
V2 + V3	*1 (3.6)*	*12/124 (9.7)*	
V1 + V2 + V3	*16 (57.1)*	*39/124 (31.5)*	
Side of pain (%): *Right / Left*	*18 (64.3) / 10 (35.7)*	*92/135 (68.1) / 43/135 (31.8)*	$\chi^2 = 0.2$; ns
Operative findings (%)			$\chi^2 = 0.3$; ns
Arterial compression	*17/25 (68.0)*	*103/129 (64.8)*	
Venous compression	*4/25 (16.0)*	*23 (14.5)*	
Mixed compression	*4/25 (16.0)*	*33 (20.8)*	

FIGURE LEGENDS

Fig. 1 | Patient flow diagram.

Fig. 2 | Pain relief at five years after first MVD of medical, surgical and no treatment after recurrence of TN. MVD, microvascular decompression; PSR, partial sensory rhizotomy; RFT, radiofrequency thermocoagulation.

Supplementary Fig. 1 | Pain outcomes of those with failure of MVD. MVD, microvascular decompression; PSR, partial sensory rhizotomy; RFT, radiofrequency thermocoagulation; GI, glycerol injection.

Supplementary Fig. 2 | Pain outcomes of those with post-MVD recurrences after previous procedures. GI, glycerol injection.

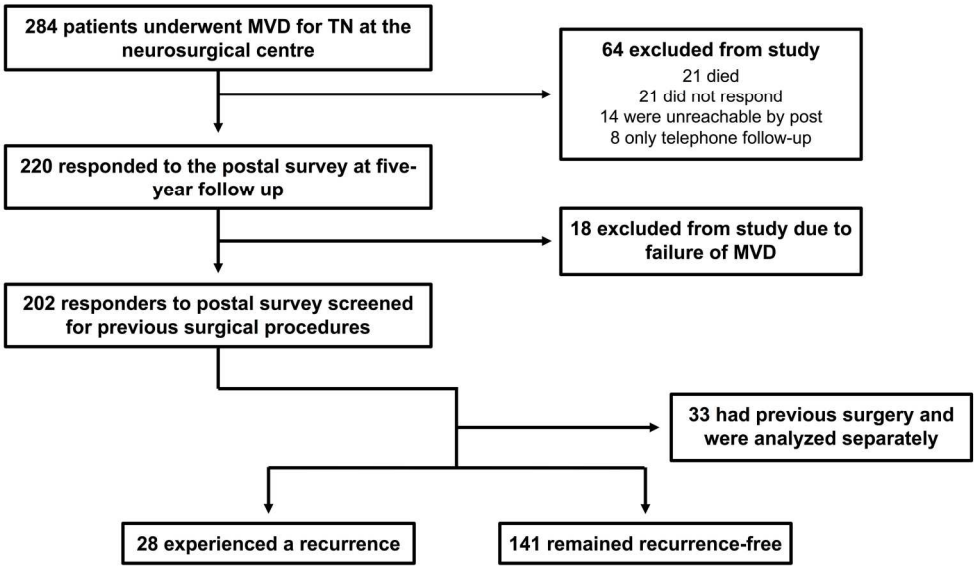


Fig. 1 | Patient flow diagram

189x110mm (300 x 300 DPI)

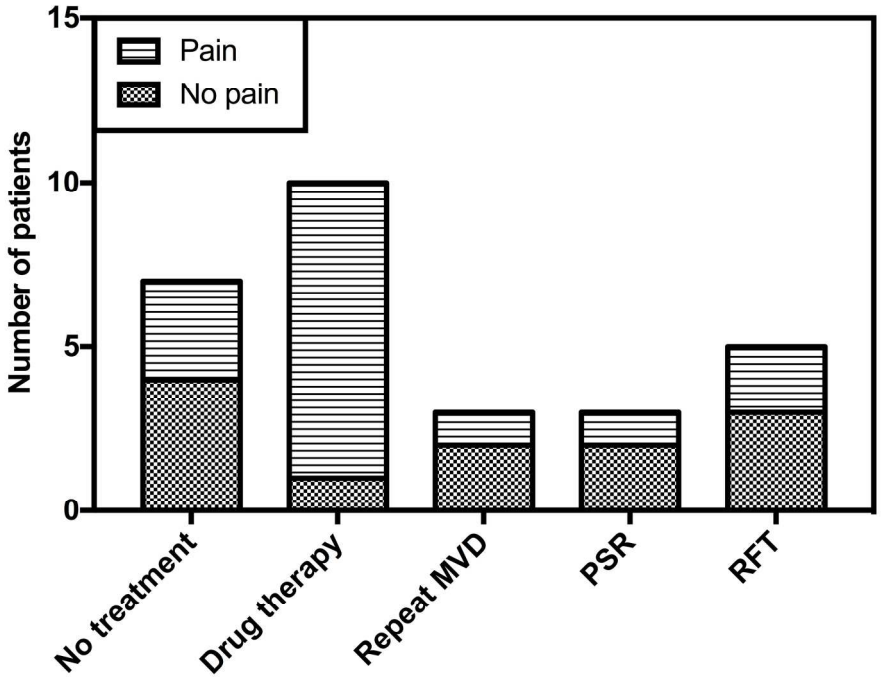
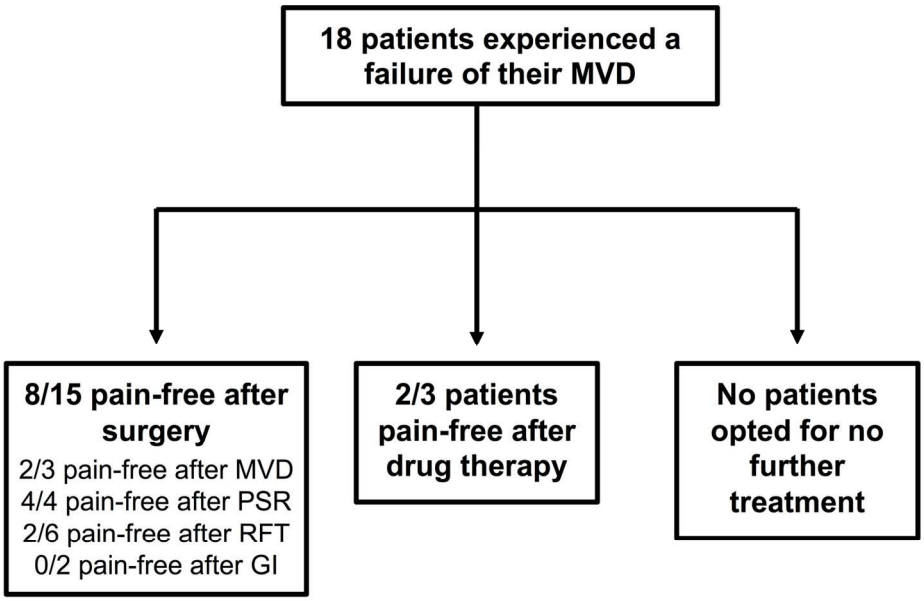


Fig. 2 | Pain relief at five years after first MVD of medical, surgical and no treatment after recurrence of TN. MVD, microvascular decompression; PSR, partial sensory rhizotomy; RFT, radiofrequency thermocoagulation

185x134mm (300 x 300 DPI)



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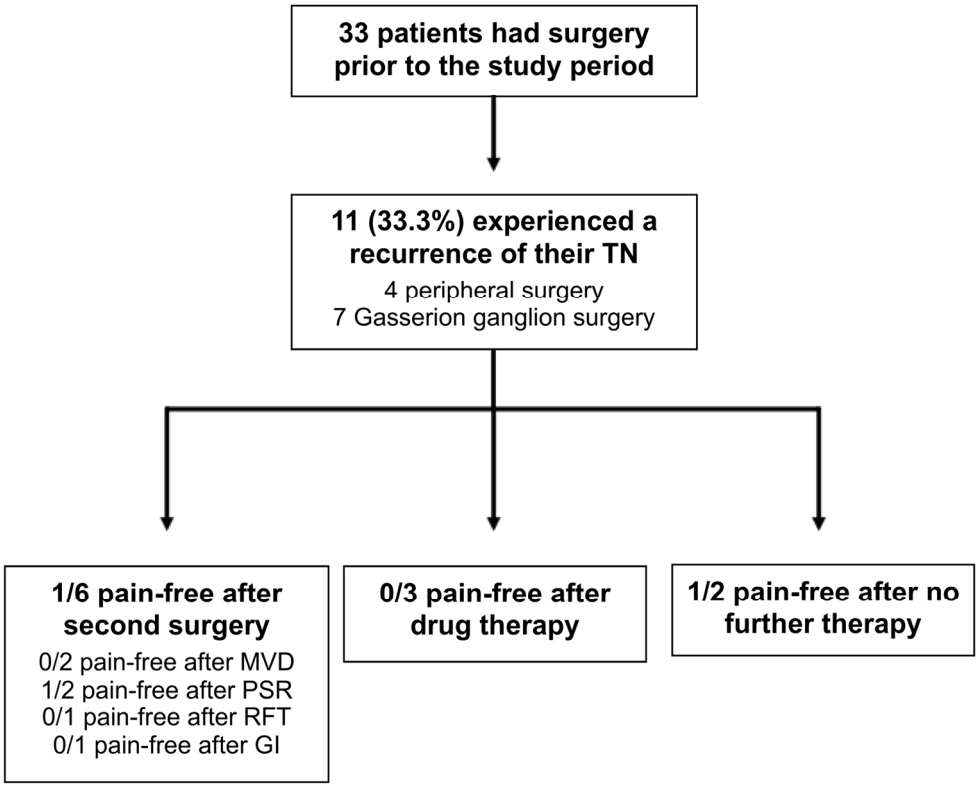

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