Trigeminal microvascular decompression for short-lasting unilateral neuralgiform headache attacks

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Running Title: Trigeminal microvascular decompression in SUNHA

Abstract

A significant proportion of patients with short-lasting unilateral neuralgiform headache attacks (SUNHA) are refractory to medical treatments. Neuroimaging studies have suggested a role for ipsilateral trigeminal neurovascular conflict with morphological changes in the pathophysiology of this disorder. We present the outcome of an uncontrolled open-label prospective single centre study conducted between 2012 and 2020, to evaluate the efficacy and safety of trigeminal microvascular decompression in refractory chronic SUNHA with magnetic resonance imaging evidence of trigeminal neurovascular conflict ipsilateral to the pain side. Primary endpoint was the proportion of patients who achieved an "excellent response", defined as 90-100% weekly reduction in attack frequency, or "good response", defined as a reduction in weekly headache attack frequency between 75% and 89% at final follow-up, compared to baseline. These patients were defined as responders. The study group consisted of 47 patients of whom 31 had SUNCT and 16 had SUNA (25 females, mean age ± SD 55.2 years ± 14.8). Participants failed to respond or tolerate a mean of 8.1 (±2.7) preventive treatments pre-surgery. Magnetic resonance imaging of the trigeminal nerves (n=47 patients, n=50 symptomatic trigeminal nerves) demonstrated ipsilateral neurovascular conflict with morphological changes in 39/50 (78.0%) symptomatic nerves and without morphological changes in 11/50 (22.0%) symptomatic nerves. Post-operatively, 37/47 (78.7%) patients obtained either an excellent or a good response. Ten patients (21.3%, SUNCT=7 and SUNA=3) reported no post-operative improvement. The mean post-surgery follow-up was 57.4±24.3 months (range 11-96 months). At final follow-up, 31 patients (66.0%) were excellent/good responders. Six patients experienced a recurrence of headache symptoms. There was no statistically significant difference between SUNCT and SUNA in the response to surgery (p=0.463). Responders at the last follow-up were however more likely not to have interictal pain (77.42% vs 22.58%, p=0.021) and to show morphological changes on the magnetic resonance imaging (78.38% vs 21.62%, p=0.001). The latter outcome was confirmed in the Kaplan Meyer analysis, where patients with no morphological changes were more likely to relapse overtime compared to those with morphological changes (p=0.0001). All but one patient who obtained an excellent response without relapse, discontinued their preventive medications. Twenty-two post-surgery adverse events occurred in 18 patients (46.8%) but no mortality or severe neurological deficit was seen. Trigeminal microvascular decompression may be a safe and effective long-term treatment for short-lasting unilateral neuralgiform headache attacks patients with magnetic resonance evidence of neurovascular conflict with morphological changes.

Keywords: short-lasting unilateral neuralgiform headache attacks; SUNCT; SUNA; microvascular decompression; trigeminal neuralgia

Abbreviations: ICHD= International Classification of Headache Disorders; MRI= magnetic resonance imaging; NVC= neurovascular conflict; OR= odd ratio; REZ: root entry zone; SUNA= Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT= Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TACs= trigeminal autonomic cephalalgias

Introduction

Short-lasting unilateral neuralgiform headache attacks (SUNHA) is an umbrella term that encompasses short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA). These rare primary headache disorders are grouped together under the trigeminal autonomic cephalalgias (TACs) given the presence of, often multiple, daily attacks of severe unilateral pain occurring in the trigeminal distribution and associated with cranial autonomic features.[1] However, the very high frequency of painful attacks, their very short duration, along with the neuralgiform quality of the pain, its triggerability by ipsilateral cutaneous or intraoral stimulations and the lack of circadian rhythmicity suggest an overlap with trigeminal neuralgia (TN).[2]

Functional imaging studies in SUNHA have shown involvement of the posterior hypothalamic region during attacks, similarly to the other TACs.[3,4] Moreover, similarly to TN, a recent large prospective cross-sectional magnetic resonance (MRI) study conducted in 159 patients with SUNCT and SUNA showed a significantly higher proportion of neurovascular contact with morphological changes on the symptomatic trigeminal nerves, compared with the asymptomatic nerves (61.4% versus 31.0%; Odds Ratio 4.16, 95% Confidence Interval 2.46-7.05; P<0.0001). The multivariate analysis of radiological predictors associated with the symptomatic side indicated that the presence of neurovascular contact with morphological changes was strongly associated with the side of the pain, suggesting that this finding may be a shared causative factor with TN.[5]

SUNHA almost invariably displays a chronic pattern either ab initio or following a short period during which the condition remits and relapses.[6] This means that a long-term preventive therapy is required for most patients. Up until recently, the preventive management of this condition was studied in small case series.[7,8] A recent large prospective open-label study conducted in 161 patients on the medical treatments of SUNCT/SUNA confirmed the efficacy of sodium channel blockers, also indicating a therapeutic overlap with TN.[9] Given the known tolerability issues of sodium channel blockers, especially at high doses often required to control SUNHA symptoms, an unknown though likely high proportion of patients become refractory to medical treatments, thereby justifying surgical approaches.

The surgical management of SUNHA has progressively moved away from destructive procedures targeting the trigeminal pathway,[10] to non-destructive invasive neuromodulation modalities, namely occipital nerve stimulation (ONS) and ventral tegmental area (VTA-DBS).[11-13] However, neuromodulation

treatments may take several weeks to months to exert their full benefits and may not lead to pain-freedom.[14] Furthermore hardware-related adverse events that occur in a variable proportion of cases, may lead to multiple surgical reinterventions.[15] This, along with the cost of the devices and the necessity of regular outpatients appointments, increase the overall treatment costs, restricting their use to a few highly specialised centres.

In view of the clinical similarities between SUNHA and TN as well as radiological evidence showing a high prevalence of trigeminal NVC in SUNHA, a few case reports and a small case series submitted SUNCT and SUNA patients to trigeminal MVD and reported positive outcomes.[16-22] Here, we analyse the safety and long term efficacy of trigeminal MVD in a large group of patients with chronic SUNHA refractory to medical management and with MRI evidence of trigeminal NVC.

Methods

This was a single-centre, non-randomised, prospective open-label study aiming to evaluate the efficacy of trigeminal MVD to medically intractable chronic SUNHA patients who had failed medical treatments and who showed ipsilateral trigeminal neurovascular conflict on MRI with dedicated trigeminal nerves sequences.[9]

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics board approval for data collection and publication was granted by Northwick Park Hospital Research Ethics Committee, Hampstead, London, UK (REC: 11/LO/1709). Written consent form was obtained from each participant.

Patient selection

Patients were recruited by a specialized headache team at the National Hospital for Neurology and Neurosurgery between 2012 and 2020. Diagnoses were made according to the International Classification of Headache Disorders 3 beta version (ICHD-3ß);[23] when subsequently applied, the diagnoses also fulfilled the ICHD-3 diagnostic criteria for chronic SUNCT or SUNA.[1] All patients had SUNCT or SUNA for at least two years and experienced highly disabling, medically refractory symptoms. There is no consensus on the definition of medically refractory SUNHA, hence the criteria proposed by Lambru and colleagues were adopted: patients who failed to respond or tolerate adequate trials of lamotrigine, topiramate, gabapentin or pregabalin and at least one of either carbamazepine or oxcarbazepine were considered refractory.[11]

All eligible patients required magnetic resonance imaging (MRI) evidence of ipsilateral trigeminal NVC and strictly unilateral side-locked headache attacks or bilateral NVC and unilateral side-alternating attacks. Consecutive patients with chronic refractory SUNHA and MRI evidence of NVC on MRI were included in the study. Otherwise, neuromodulation approaches namely occipital nerve stimulation (ONS), or central ventral tegmental area (VTA) deep brain stimulation (DBS) were considered.

Outcome measures and follow-up

Pre-and post-operative outcome data were collected in a predefined study questionnaire and recorded prospectively. These included frequency, severity, and duration of attacks, which were collected using a headache chart designed to capture the individual headache attacks; reduction/discontinuation of preventive medications and surgery-related adverse events. Headache frequency was defined as number of SUNHA attacks per day. Headache severity was measured on the verbal rating scale (VRS) for pain (0 being no pain and 10 being the worst pain imaginable). The Headache Impact Test Score (HIT- 6) was used to assess disability of headache symptoms. This score has been widely used in the assessment of primary headache disorders including TACs.[11,24]

The immediate postoperative relief of symptoms was graded as excellent, good, or poor during the first week after surgery. The primary outcome of this study was the proportion of patients who achieved an "Excellent response", defined as 90-100% reduction in SUNCT or SUNA weekly attack frequency or a "Good response", defined as a reduction in weekly headache attack frequency between 75% and 89% at final follow-up compared to baseline. "Poor response" was defined as a reduction of less than 75% in SUNCT or SUNA weekly attack frequency and "No response" was defined as a lack of any noticeable reduction in attack frequency compared to baseline.[25] Secondary, exploratory outcomes included: change in headache severity using VRS; change in headache attacks duration; change in headache load (HAL), a composite score defined as a $\sum$ [severity (verbal rating scale)] x [duration (min)] of all attacks over a 2-week period.[12]

Patients were seen at 3-monthly intervals post-surgery over the first year, 6-monthly over the second year and once annually thereafter. Timing of additional appointments was dependent on clinical condition. The efficacy outcomes were assessed immediately after surgery and at the last study follow-up assessment in December 2020. Post-surgical complications were evaluated by the neurosurgical team acutely and by the neurology team during the study follow-up period.

MRI protocol

All SUNHA patients who attend our headache service, including those who were candidates for trigeminal MVD in this study, undergo MRI scans with high-resolution sequences of the trigeminal nerves. The MRI examinations are performed on a 1.5-Tesla GE Signa Excite (GE Medical Systems, Milwaukee), 1.5-Tesla Siemens Avanto or 3.0-Tesla Siemens Trio (Siemens, Erlangen) MRI scanner. The standard imaging protocol includes high spatial and nerve-cistern contrast resolution imaging acquisitions of the cisternal segments of the trigeminal nerves and vessels, with 3D Fast Imaging Employing Steady-State Acquisition (FIESTA; TE: 1.5ms, TR: 4.9ms, NEX: 4), 3D Constructive Interference in Steady State (CISS; TE: 5.3ms, TR: 10.6ms, Excitations: 1), or 3D Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE; TE: 132ms, TR: 1000ms, Excitations: 2). Neurovascular contact is defined on the analysis of imaging by no perceptible cerebrospinal fluid (CSF) signal intervening the silhouette of the vascular structure (arterial or venous) and the cisternal segment of the trigeminal nerve.

The trigeminal nerve on the side of the pain was defined as the symptomatic nerve; the trigeminal nerve contralateral to the side of the pain was defined as the asymptomatic nerve. In patients with side alternating unilateral head pain, both trigeminal nerves were considered symptomatic.

In view of the ongoing debate about the definition and boundaries of the zone where peripheral myelination transitions to central myelination ('root entry zone' or 'transition zone'), sites of NVC on the trigeminal nerve were divided in three segments, namely proximal, middle and distal.[26,27] In addition to the presence or absence of contact and involvement of the REZ, we also assessed for the degree of neurovascular contact and type of vessel involved. The degree of contact was graded as: simple contact, distortion or atrophy. Distortion was defined as indentation or displacement of the trigeminal nerve at the site of the neurovascular contact. Atrophy was defined as reduced volume of the trigeminal nerve at the site of the neurovascular contact. As per recent guidelines of the European Academy of Neurology, the degree of NVC was classified as with (distortion, indentation, atrophy) or without (simple contact) morphological changes.[28] All MRI scans were reviewed by an expert neuroradiologist (ID) and neurosurgeons (LZ and NK) who performed the operation. Assessors were blind to the side of the pain.

Surgical procedure

A modified Jannetta procedure was used as follows: under anaesthesia, the subject was placed in the park-bench position with the neck flexed. The head was placed in Mayfield pins three-point fixation and

rotated slightly away from the affected side. A retro-sigmoid approach was utilized with a 6cm skin incision behind the mastoid and a small craniectomy, exposing the junction of the lateral and sigmoid sinus. The dura was opened in a T fashion and CSF released to relax the cerebellum. Under the operating microscope, arachnoid adhesions and bridging veins were divided to expose the trigeminal nerve. The arachnoid surrounding any conflicting artery was divided and the vessel mobilized away from the nerve. A Teflon wedge was used to prevent the vessel from returning to its original position and was held in place with a spot of fibrin glue.

Statistics

All statistical analyses were conducted with Stata (Version 11.2). In descriptive analysis, continuous variables were summarized using mean and standard deviation, or median and range, depending on data distribution. Categorical variables were using percentages. When appropriate comparative assessments between various subgroups were carried out using Chi-squared tests or Fisher's exact tests for categorical variables or independent t-test for numerical variables. No multiplicity adjustment was applied. Therefore, statistically significant p-values (p-value less than 0.05) should be interpreted with caution.

For the primary outcome of interest, Kaplan-Meier relapse free survival (RFS) curve were computed overall and according to diagnosis (SUNA and SUNCT), interictal pain (Yes/No), and MRI morphological changes (Yes/No) and were compared using log-rank tests.[29] Time was defined as the time elapsed between date of relapse or last follow-up and date of surgery. Patients who did not relapse or were lost to follow up were censored. Hazard ratios and corresponding 95% confidence intervals were derived using univariate Cox regression model. Relapse free rates were estimates using life table method.[30]

Data availability

The data that support the findings of this study are available from the corresponding author.

Results

Patients baseline characteristics

Forty-seven SUNCT and SUNA patients (31 SUNCT, 66.0%; 25 females; mean ± SD age 55.2 years ± 14.8) underwent trigeminal MVD. Patient demographics and baseline headache characteristics are shown in Table 1. All but six patients (87.2%) reported at least one of the pain sites in the distribution of the ophthalmic division of the trigeminal nerve (V1). Most patients (89.4%) experienced spontaneous

attacks and attacks triggered by cutaneous and/or intraoral stimulation. Only one patient reported refractory periods following triggered attacks. Other primary headaches, namely chronic migraine (CM; n=9) and chronic cluster headache (CCH; n=8) were present in 17 patients.

All patients except for one were considered medically refractory.[11] This patient opted to undergo MVD after having failed to respond to two preventive treatments only because of the severe disability of their headache condition. The mean (±SD) number of medical treatments failed by our patient group at the time of the surgery was 8.1 (±2.7). Intravenous (IV) lidocaine was tried by 22 patients and found effective in controlling the SUNCT/SUNA symptoms in 17 of them (77.3%), though efficacy was short-lasting. Two patients also had incomplete response to neuromodulation (ONS or VTA-DBS) at baseline. At the time of surgery all patients were taking preventive treatments. The mean (±SD) study cohort HIT-6 score at baseline was $69.6\ (\pm\ 6.2)$; the HIT-6 scores at baseline in 38 patients (80.9%) was classified within the category of severe disability (HIT-6 $\geq$ 60).

Table 2 summarises the MRI finding pre-operatively. The neuroradiologist and neurosurgeons agreed on the MRI findings for all patients but one, where there was disagreement whether the vessel causing conflict was artery or vein. NVC ipsilateral to the pain side was found in all patients. Out of 47 patients, 50 symptomatic trigeminal nerves were analysed (three patients had unilateral side alternating painful attacks). An arterial conflict either by the superior cerebellar artery (SCA) only (n=47) or by the anterior inferior cerebellar artery (AICA) only (n=2) or by a mixture of the two arteries (n=1) was found to conflict with all the symptomatic trigeminal nerves. Trigeminal neurovascular conflict with morphological changes was found in 78% (n=39/50) of the symptomatic nerves. In 20 of the 39 symptomatic nerves with NVC (51.3%), the morphological changes included nerve atrophy, which involved the proximal nerve segment in 18 cases and distal in two cases. NVC without morphological changes was present in 22% (n=11/50) of the symptomatic nerves.

All patients underwent trigeminal MVD. Intraoperatively, the neuroimaging findings were confirmed. In the patient for whom there was lack of agreement between the neurosurgeon and neuroradiologist, both an artery and a vein were found intra-operatively to contact the trigeminal nerve. Figure 1 illustrates an example of trigeminal NVC with morphological changes and intraoperative photographs pre- and post-MVD.

Primary and secondary efficacy outcomes

Post-operatively, 37 patients obtained an excellent or good response (78.7%); of these, 34 patients reported an excellent response (72.3%) and three patients reported a good response (6.4%). These three patients obtained respectively a mean headache attacks frequency reduction from 84 to 21/week, from 42 to 7/week and from 91 to 14/week. Their mean attacks intensity was also reduced post-operatively from 9/10 to 6/10, from 10/10 to 8/10 and from 7/10 to 4/10 respectively. Ten patients (21.3%, SUNCT=7, SUNA=3) reported no post-operative improvement.

Most responders obtained an excellent or good improvement immediately post-operatively (n=35/37, 94.6%). However, two patients reported either a slightly delayed or a gradual improvement of the headache symptoms. One SUNA patient began noticing a reduction in attacks frequency within two weeks post-operatively, which reached 80% reduction compared to baseline at month 3 and 90% attacks reduction from month six post-surgery onwards. The time to response for the second patient (SUNCT) was four weeks. At that time, he experienced a 70% attacks' reduction compared to baseline. He became pain-free three months later (month 4 post-surgery).

The mean post-surgery follow-up was 57.4 ±24.3 months (range 11-96 months). At final follow-up, 31 patients (66.0%) remained excellent/good responders (Excellent responders=28; good responders=3). Six patients had a recurrence of SUNHA symptoms (SUNCT=3, SUNA=3) (Figure 2). Twenty-five of the 28 excellent responders (89.3%) remained off any medications for the SUNHA at the final follow-up.

Recurrence was defined as meeting the criteria for "poor or no response" after an immediate/delayed excellent or good response post-MVD was achieved. The annual rate of recurrence of SUNHA after MVD was estimated by life-table analysis. The annual risk of recurrence at year 1 was 5.6%, at year 3 was 12.3%, at year 4 it was 16.3% and at year 5 it was 23.4% (Figure 3). Post-operative MRI scans in those in whom the condition relapsed, confirmed satisfactory trigeminal decompression, hence a second operation was not offered. Interestingly, in three patients, the relapsed SUHNA symptoms were almost completely controlled after treating them with oral medications, respectively carbamazepine 800mg/day, lamotrigine 100mg/day and lamotrigine 200mg/day, that were ineffective or marginally effective pre-MVD. Two patients were assessed in our multidisciplinary neuromodulation clinic and VTA-DBS was offered. One patient reported a 50% headache improvement after DBS and another patient did not find the treatment effective. One patient remained non responder to medical treatments after headache attacks recurrence.

The Kaplan-Meier analysis showed no statistically significant difference in relapse from treatment success overtime between SUNCT and SUNA (Figure 4a), and between patients with or without interictal pain (Figure 4b). However, patients with NVC without morphological changes were more likely to relapse compared to patients with NVC with morphological changes (p=0.0001) (Figure 4c). Similarly, responders to trigeminal MVD at the last follow-up, were more likely not to have interictal pain (p=0.021) and to show morphological changes in one or both nerves on the MRI (p=0.001) (Table 3).

Table 4 summarises the changes in secondary outcomes, namely the mean headache severity, duration and in the headache load at the final follow-up post-MVD. There was a statistically significant reduction in all three outcomes. The HIT-6 score was reduced from 69.6 ($\pm$ 6.2) at baseline to 50.7 ($\pm$ 13.4) at the final follow-up. Furthermore, the percentage of patients with severe disability was reduced from 80.9% (n=38) to 21.3% (n=10), with most patients' final HIT-6 scores showing no headache-related impact to their quality of life.

Bilateral microvascular decompression outcome

Three patients had side alternating SUHNA attacks. One patient had bilateral trigeminal NVC with and without morphological changes. She underwent the first MVD, which controlled the left-sided attacks by 90% and two years later she had a right-sided MVD, which controlled the right-sided attacks by 99%. No adverse events were reported. The second patient had side alternating headache attacks that were predominantly left-sided. Her MRI of the trigeminal nerves showed bilateral NVC, both with morphological changes. She underwent a left trigeminal MVD which led to an immediate reduction from a mean attack frequency of 91 to 14/week (85% improvement). Eleven months later she underwent a right-sided trigeminal MVD, which led to an immediate reduction of the right-sided attacks from a mean of 70 attacks to a mean of 21 attacks/week (70% improvement). The severity of her attacks was also reduced post-operatively from a mean of 7/10 to a mean of 4/10. The patient developed mild hearing loss after the second surgery. The third patient underwent left-sided MVD, which led to pain-freedom from the left sided attacks. Eighteen months later he underwent a right-sided MVD, which led to pain freedom from the right-sided attacks. After the second MVD, he experienced CSF leak which was successfully repaired.

Surgical complications

Twenty-two post-surgery adverse events occurred in 18 patients (46.8%). Four patients developed a CSF leak which was surgically repaired. Three patients developed mild to moderate neuropathic pain on the

wound site, which persisted at final follow-up. One patient developed transient facial numbness and five persistent (mild/moderate) facial numbness. One patient developed post-operative transient vertigo. One patient developed a new daily persistent headache. One patient developed lingual numbness and two patients developed mild hearing loss. One patient reported a worsening of a pre-existing bilateral tinnitus. Over half of patients (61.7%, n=29) experienced no complications post-surgery.

Discussion

SUNHA is a rare and diagnostically challenging condition, due to its clinically overlap with the TACs but also with TN.[2] SUNHA also poses significant treatment difficulties. A recent large prospective study shed some light upon the potentially effective medical preventive options for these conditions, outlining a treatment algorithm to support clinical practice.[9] However, despite advances in the medical management of SUNHA, in a significant proportion of patients the symptoms become medically-refractory over time, hence justifying the use of more invasive approaches. Open-label data on the use of ONS and VTA-DBS have yielded promising long-term results in refractory SUNHA.[13,12] However, neuromodulation is an expensive technology, which often does not provide complete headache relief and requires numerous postoperative visits for adjustment of the stimulation parameters.[22]

Previous case reports and small case series have suggested a beneficial effect of trigeminal MVD in SUNHA.[16-22] Our study provides the largest evaluation of long-term efficacy and safety of trigeminal MVD in chronic refractory SUNHA. The surgical procedure appears to be safe and effective for the management of patients in whom the symptoms are otherwise medically intractable and high-resolution MRI sequences of the posterior fossa shows evidence of a vascular conflict with the symptomatic trigeminal nerve. Symptomatic improvement was accompanied by significant improvement in headache disability.

Our results are similar to those in a small case series of nine SUNCT/SUNA patients treated with trigeminal MVD. Six out of the nine patients (67%) in that study became immediately symptoms-free after surgery and remained so for the follow-up duration (mean 22.2 months, range: 9-32 months).[21] The consistency of positive results in two series of patients coming from different centres suggest that this procedure may have an important role in the management of refractory forms of SUNCT and SUNA. Furthermore, our study suggested the absence of any significant differences in the surgical outcome between SUNCT and SUNA. Although the sample size of this study does not allow a statistically conclusive comparison between the two patients groups, these findings, along with the absence of

clinical and radiological differences demonstrated in recent studies, support the notion that SUNCT and SUNA may be different manifestations of the same clinical entity and that consideration may ultimately need to be given to abandoning their separation.[5,6]

In our cohort, most patients reported an immediate headache relief post-operatively. However, a progressive or slightly delayed response may seldom happen, suggesting a wait of up to four months before considering patients, non-responders. Trigeminal MVD led to improvements in frequency, severity and attack duration as derived from the reduction of the "headache load". In fact, the most likely outcome in responders was complete pain relief. Pain freedom is a treatment outcome not normally explored in trials testing treatments for primary headache disorders.[31] This is because the lack of complete understanding of their pathophysiological mechanisms has prevented the development of treatments that can remove the offending mechanism. In TN, NVC with morphological changes on the symptomatic nerve root plays a central role in the pain mechanisms in the majority of patients[32] and removing the offending vessel surgically with trigeminal MVD leads to sustained long-term pain-freedom, making MVD the closest possible treatment to a "cure", at least for the classical purely paroxysmal form.[25]

Some studies have shown that trigeminal nerve atrophy is more likely to be associated with better MVD outcomes.[33] However, in a small series of TN patients with atrophy of the distal trigeminal nerve, MVD outcomes appeared worse compared to the outcomes of MVD with atrophy of the proximal nerve segment.[34] In our series, nerve atrophy was associated with a positive MVD outcome in most cases, albeit that only two patients had distal trigeminal nerve atrophy.

MRI findings in SUNHA have also suggested that trigeminal NVC in involved in the aetiology of SUNHA[5] and the sustained outcome of trigeminal MVD demonstrated in this study may confirm the importance of trigeminal NVC in the pathophysiology of SUNHA at least for the majority of patients with NVC on MRI. This peripheral drive may be the predominant mechanism responsible for the neuralgiform type of pain, the very short duration and high frequency of attacks, the triggerability of the attacks and the refractory period, which are unique characteristics for these disorders amongst the TACs and constitute the core of the clinical overlap with TN. However central mechanisms are also likely to play a pivotal role in both SUNHA and TN. Functional neuroimaging studies suggest an important role for the hypothalamus in SUNHA.[3,4] Arguably hypothalamic networks may also be relevant in TN

pathophysiology, though supportive evidence is still lacking mainly due to dearth of appropriate functional neuroimaging studies in this disorder. Nonetheless, one of the cornerstone clinical characteristics of the TACs by which these disorders are purported to differ from TN, is the association between head pain and ipsilateral cranial autonomic signs and symptoms, a hallmark of hypothalamic dysregulation. However, several studies have reported that TN purely paroxysmal or with concomitant persistent pain can be associated with cranial autonomic features, suggesting that there may be an overlap of the central pain mechanisms in these conditions.[35-38] Ultimately, SUNCT, SUNA and TN may share a unified pathophysiological model characterized by different degrees of interaction between peripheral and central mechanisms, namely unilateral focal demyelination of the trigeminal sensory root and ipsilateral trigemino-hypothalamic dysfunction. This interaction may be responsible for the phenotypical differences and response to treatments of these conditions. Its noteworthy that three patients in this series had unilateral side-alternating SUHNA attacks. Unilateral side-alternating attacks in SUNHA occur more frequently than in TN (12-13.5% vs 1.7-5%). [6,8,39] However patients with either conditions seem to benefit from bilateral trigeminal MVD as per our data in SUNHA and larger TN series.[25] These clinical and therapeutic similarities may suggest the relevance not only of unilateral but also of bilateral peripheral and perhaps central mechanisms. Indeed, bilateral hypothalamic activation during SUNCT attacks in functional MRI studies has been reported,[4] supporting the link between pathophysiological mechanisms involved and pain laterality.

The importance of central pain mechanisms in SUNHA may be reflected by the proportion of patients in our study that did not respond to the treatment or relapsed overtime (34%). The relapse free survival rate analysis demonstrated a pain recurrence in 5.6% of patients within the first two years post-MVD, which increased to 23.4% at year 5, though no relapses occurred from year 5 to the last follow-up. Although our sample was too small to compare the relapse rate to the pivotal TN MVD study,[25] it seems that the risk of relapse may be higher in SUNHA than in TN up to five years post-operatively, before it subsequently settles in both conditions.

The higher relapse rate in SUNHA compared to TN could be secondary to the persistence of central hypothalamic impaired pathways in some patients, which may cause an abnormal reactivation of the trigemino-autonomic circuits even in the absence of a peripheral drive.

Amongst factors predictive of poor response or relapse, the presence of interictal continuous pain has emerged in our analysis as a potential negative prognostic factor. The presence of interictal pain in between the painful paroxysms is a well-known TN clinical characteristic occurring in 49% of TN patients[40] and associated with poor response to medical and surgical treatments.[41] The relevance of the presence of interictal pain is reflected in the classification, where TN with interictal pain constitutes a defined sub-type of TN with treatments implications.[1] Furthermore, a recent study reported an association between interictal continuous facial pain in TN and trigeminal nerve root atrophy. This finding may suggest that axonal loss in denervated atrophic nerves may at least partly explain the poor outcome of MVD in this group of TN patients.[42] SUNHA with interictal pain (48%) is as frequent as TN with interictal pain (49%).[6,40] Similarly to TN, this study suggests that SUNHA with interictal pain patients may respond less well to trigeminal MVD compared to the form without interictal pain. However, a significant association of interictal pain and nerve atrophy on MRIs was not found in our series, though a volumetric trigeminal nerve root analysis was not conducted in our study. Should this treatment response difference be confirmed in future studies, it may justify sub-classifying SUNHA in two forms: purely paroxysmal and with concomitant constant facial pain.

Trigeminal NVC with the symptomatic nerve in TN and SUNHA is a common finding. However only NVC with morphological changes are involved in the aetiology of these conditions.[5,32] It is therefore plausible to assume that the lower percentage of responders and higher rate of relapse to MVD over time observed in SUNHA patients with NVC without morphological changes, may be explained by the lack of pathophysiological relevance of NVC in these patients, highlighting the importance of patients selection and of obtaining good quality trigeminal nerves images when planning surgery. On the other hand, a significant minority of our long-term responders had simple contacts on the symptomatic trigeminal nerves. Post-MVD data in TN also suggest that patients with simple contacts on MRIs can achieve and maintain excellent long-term post-operative outcomes.[25]

Our earlier study demonstrated that presence of neurovascular contact with morphological changes was strongly associated with the side of the SUNHA pain thereby suggesting a central role for this in the aetiology of SUNCT and SUNA.[5] The favourable outcome of trigeminal MVD demonstrated in this study further supports the importance of neurovascular conflict with morphological changes in the aetiology of SUNHA. Focal demyelination of the trigeminal sensory root caused by vascular compression may participate in SUNHA pain mechanisms. Similarly to TN, vascular compression generates spontaneous ectopic impulses, ephaptic cross talking activities between fibers mediating light touching (A-β) and

nociceptive fibers (A-δ) and abnormal activation of wide dynamic range neurons,[43] which may explain the origin of symptoms that differentiate SUNHA phenotype from the other TACs, namely very short-lasting spontaneous stabbing pain episodes, the pain triggered by innocuous stimulation of the symptomatic trigeminal territories and the refractory period between triggered attacks.[2]

Post-operative side effects of MVD in our series were higher compared to the TN literature.[44] However, serious and persistent side effects were rare. It is possible that the higher rate of side effects including the mild and transient ones was a result of the careful and systematic post-operative assessment that these patients underwent as part of the study.

The main limitation of this study is the lack of a control arm. Although there is undoubtedly a placebo effect for surgical headache treatments, it is unlikely that our findings can be explained by this alone. Furthermore, ethical issues have so far prevented the design of sham surgery in trigeminal MVD literature.

In conclusion, trigeminal MVD is the closest treatment to a symptomatic "cure" that can be offered for chronic refractory SUNHA. The treatment is effective in most patients with sustained effects over time and low relapse rate. It may be possible that patients with interictal pain and without MRI findings of morphological changes response less well to MVD.

We therefore propose that all SUNHA patients undergo MR imaging of the prepontine cistern to rule out pathological processes in the region as well as to examine for neurovascular conflict. Based on our data, trigeminal MVD may be offered as a first procedure to those patients with neurovascular conflict who remain symptomatic or suffer from significant side-effects despite optimal medical management. Patients with morphological changes may experience a better outcome, though their absence does not rule out the possibility of symptoms improvement. As with every neurosurgical procedure, MVD carries risks. Nevertheless, in experienced centers, the risk of serious harm is low. Neuromodulation may be reserved for patients without MRI evidence of trigeminal neurovascular conflict or for those with conflict who have not responded to MVD or in whom this approach is contraindicated.

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Competing interests

GL has received speaker honoraria, funding for travel and has received honoraria for participation in advisory boards sponsored by Allergan, Novartis, TEVA, Eli Lilly and Lundbeck. He has received speaker honoraria, funding for travel from electroCore, Nevro Corp. and Autonomic Technologies. SL has received speaker honoraria and has received honoraria for participation in advisory boards sponsored by Allergan, Novartis, TEVA and Eli Lilly. AL, SC, ID, KR and NK have nothing to declare. LZ has received speaker honoraria and consulting fees from Medtronic and Boston Scientific. MSM reports grants, personal fees and honorarium for serving on advisory board from Allergan, Novartis, Eli Lilly, TEVA, Abbott, Medtronic, electroCore and Salvia, outside the submitted work; in addition, Dr. Matharu has a patent WO2018051103A1 issued.

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Figure legends:

Figure 1 High resolution magnetic resonance imaging of the cerebellopontine angle and intraoperative views of a trigeminal neurovascular conflict treated with microvascular decompression. A. Axial and Coronal 3T MRI 0.5mm volumetric SPACE sequence: detail of left cerebellopontine angle. **B.** Images reproduced from A with trigeminal nerve (V) highlighted in yellow, branches of superior cerebellar artery (SCA) in red and cisternal veins in blue. The atrophic trigeminal nerve is distorted laterally and inferiorly by a loop of the SCA. **C, D and E:** Intraoperative photographs (labelled in bottom panels) during left microvascular decompression. **C:** neurovascular conflict between the left SCA and V, confirming the above MR findings. **D:** The SCA is mobilised towards the tentorium (Tent) and held in place with a Teflon patch (Tef). **E:** The Teflon patch is secured with fibrin glue (Fib). VIII: eighth cranial nerve; R: retractor on cerebellum.

Figure 2 Kaplan–Meier analysis of success of microvascular decompression for Short-lasting neuralgiform headache attacks.

Figure 3 Recurrence of SUNHA in patients with postoperative relief after microvascular decompression. SUNHA: short-lasting unilateral neuralgiform headache attacks.

Figure 4 Kaplan–Meier analysis of difference in success of microvascular decompression for (A) SUNCT vs SUNA; (B) SUNHA with and without interictal pain; (C) SUNHA with and without morphological changes.

Table 1 Descriptive summaries of demographic and clinical data (n=47)

Age, years	55.2 ± 14.8 [22–85]
Sex	
Female	25 (53.2%)
Male	22 (46.8%)
Diagnoses	
Chronic SUNCT	31 (66.0%)
Chronic SUNA	16 (34.0%)
Duration of chronic pattern at the time of MVD / years	9.4 (±4.5) [5–25]
Headache laterality	
Right	31 (66.0%)
Left	13 (27.6%)
Side alternating	3 (6.4%)
Headache distribution	
V1	11 (23.4%)
V2	3 (6.4%)
V1-V2	22 (46.8%)
V2-V3	3 (6.4%)
V1-C2	2 (4.3%)
V1-V2-V3	4 (8.5%)
V1-V2-C2	2 (4.3%)
Mean number of daily attacks	123.8 (± 609) [4–3600]
Mean attack severity (0–10)	8.8 (±1.4) [4–10]
Mean attack duration (seconds)	160.4 (±518.8) [1–3600]
Spontaneous and/or triggered attacks	
Spontaneous and triggered	42 (89.4%)
Spontaneous only	2 (4.3%)
Triggered only	3 (6.4%)
Refractory period	
No	44 (93.6%)
Yes	1 (2.1%)
Not applicable	2 (4.3%)
Interictal pain	
No	31 (66.0%)
Yes	16 (34.0%)
Co-existent headache types	
Chronic migraine	9 (19.1%)
Cluster headache	8 (17.0%)

Values are presented as mean (±SD) [range] or *n* (%). V1: Cutaneous territory innervated by the first division of the trigeminal nerve; V2: second division of the trigeminal nerve; V3: third division of the trigeminal nerve; C2: second cervical root

Table 2 Descriptive summary of MRI characteristics of trigeminal neurovascular conflicts

	Symptomatic nerve (n=50) N (%)	Asymptomatic nerve (n=44) N (%)
Degree of arterial conflict		
With morphological changes	39 (78.0%)	6 (13.6%)
Proximal nerve segment	30 (60.0%)	4 (9.1%)
Without morphological changes	11 (22.0%)	10 (22.7%)
Proximal nerve segment	5 (10.0%)	5 (11.4%)
Arterial conflict only	36 (78%)	10 (22.7%)
Mixed arterial and venous conflict (artery ≥ vein)	12 (24.0%)	2 (4.5%)
Mixed arterial and venous conflict (vein > artery)	2 (4.0%)	0 (0%)
Total	50 (100%)	12 (27.3%)
Degree of venous conflict		
With morphological changes	5 (10.0%)	1 (2.3%)
Proximal nerve segment	4 (8.0%)	0 (0%)
Without morphological changes	9 (18.0%)	14 (31.8%)
Proximal nerve segment	7 (14.0%)	4 (9.1%)
Venous conflict only	0 (0%)	11 (25.0%)
Mixed arterial and venous conflict (vein > artery)	2 (4.0%)	0 (0%)
Mixed arterial and venous conflict (artery ≥ vein)	12 (24.0%)	2 (4.5%)
Total	14 (28.0%)	13 (29.5%)

N= number; REZ: root entry zone

Table 3 Preoperative clinical and MRI differences between responders and non-responders (n = 47)

	Responders N (%)	Non-responders N (%)	Total N (%)
SUNCT	21 (67.7%)	10 (32.3%)	31 (66.0%)
SUNA	10 (62.5%)	6 (37.5%)	16 (34.0%)
Δ proportion of responders (95% CI); p-value	5.24% (−23.6% to −34.1%); p = 0.719		
Female	10 (60.0%)	15 (40.0%)	25 (53.2%)
Male	16 (72.7%)	6 (27.3%)	22 (46.8%)
Δ proportion of responders (95% CI); p-value	−12.73% (−39.5% to 14.01%); p = 0.358		
Interictal pain	7 (43.8%)	9 (56.2%)	16 (34.0%)
No interictal pain	24 (77.4%)	7 (22.6%)	31 (66.0%)
Δ proportion of responders (95% CI); p-value	3.36% (−5.3% to − 62.1%); p = 0.021		
MRI morphological changes	31 (79.5%)	8 (20.5%)	39 (78.0%)
No MRI morphological changes	3 (27.3%)	8 (72.7%)	11 (22.0%)
Δ proportion of responders (95% CI); p-value	5.84% (−86.5% to −30.3%); p = 0.001		

CI: confidence interval; Δ : difference; N: number; SUNCT**:** short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features.

Table 4 Secondary efficacy and headache-related disability outcomes post-MVD (n = 47)

	Pre-MVD	Post-MVD (last F/U)	p-value
Mean severity (VRS)	8.9 (±1.44) [4–10]	7.9 (±2.3) [4–10]	p = 0.030
Mean duration (seconds)	160.7 (±523.93) [1–3600]	43.75 (±62.17) [1–250]	p = 0.034
Mean headache load	530.0 (±934.58) [4–3750]	58.3 (±210.22) [1–962]	p = 0.001
Mean HIT-6 score	69.6 (± 6.2) [57–78]	50.7 (±13.4) [36–78]	p = 0.0001

Values are presented as mean (±SD) [range]. F/U: follow-up; HIT-6: headache impact test-6; MVD: microvascular decompression; SD: standard deviation; VRS: verbal rating scale

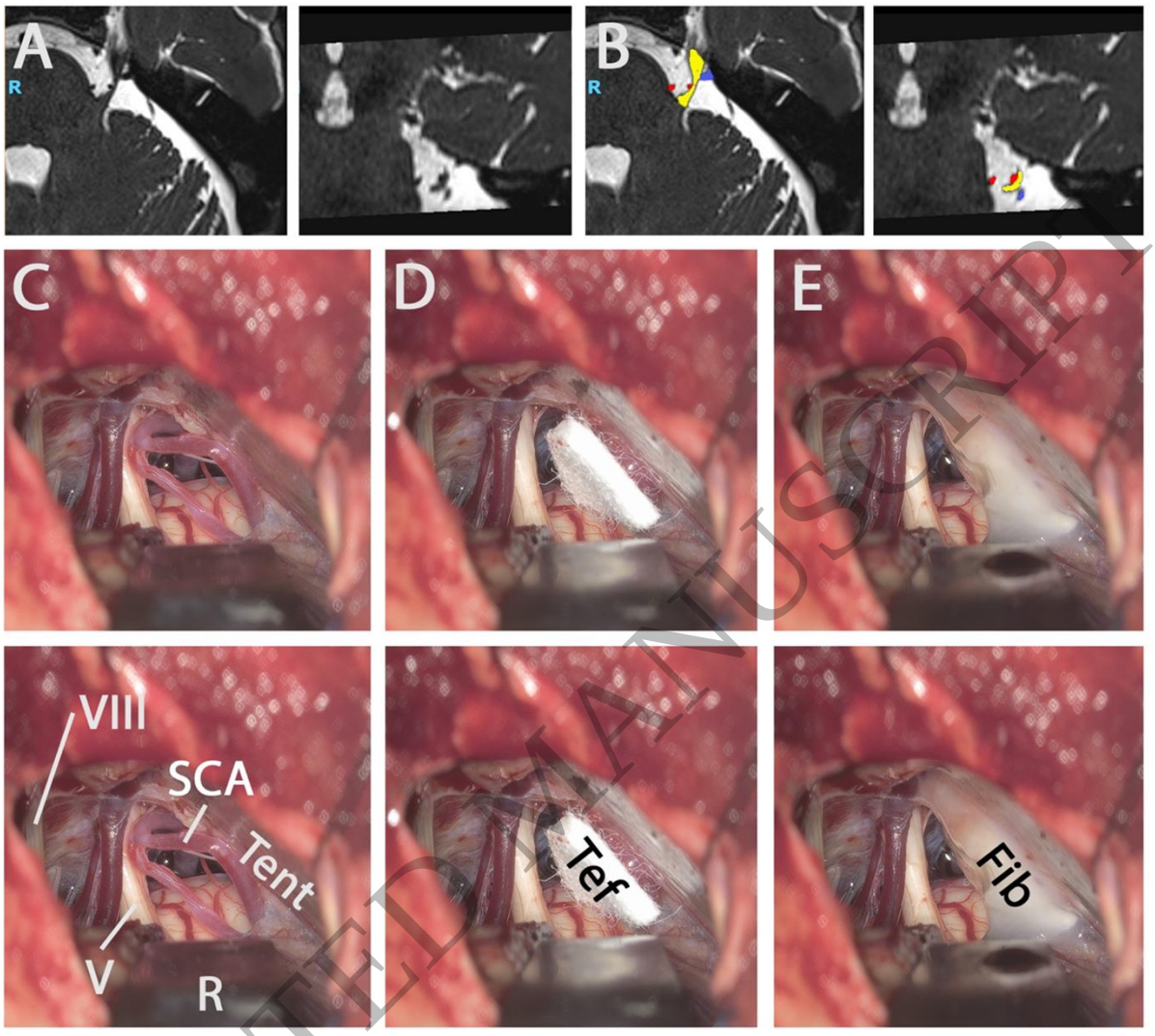

Figure 1
160x144 mm (9.1 x DPI)

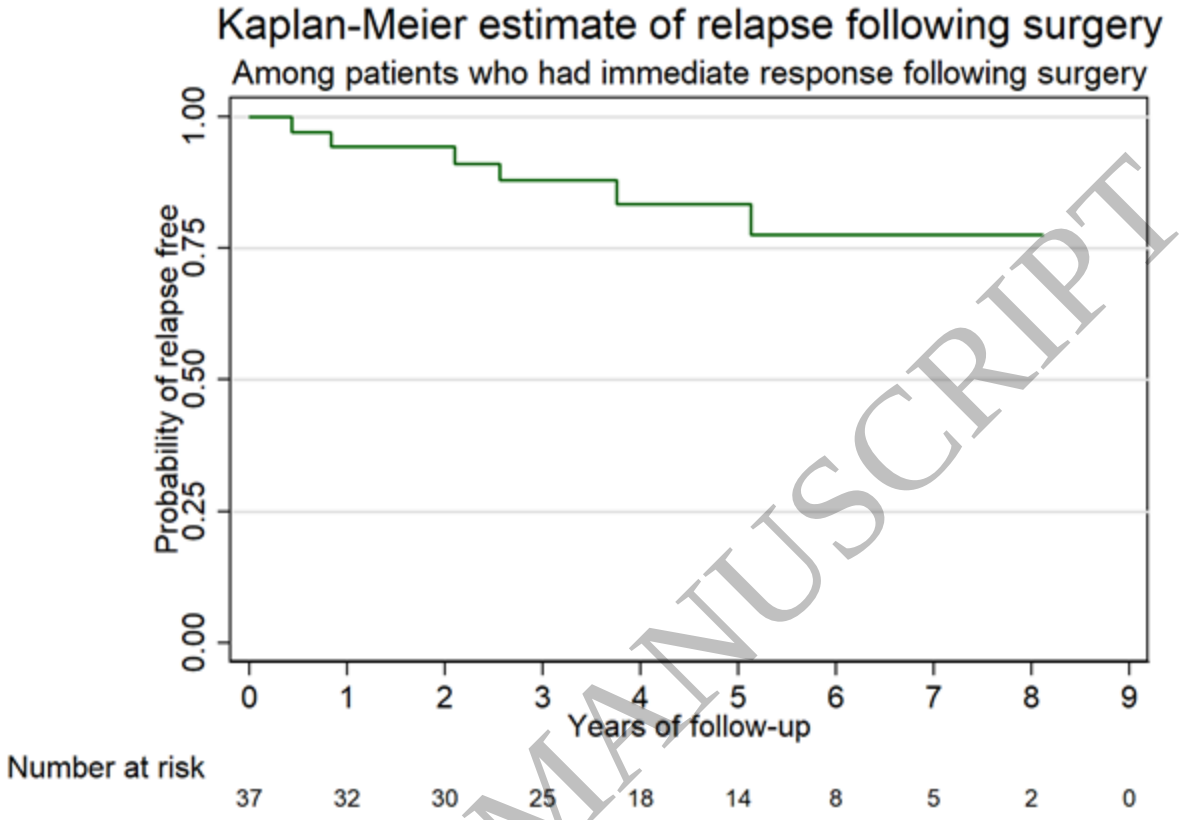

Figure 2
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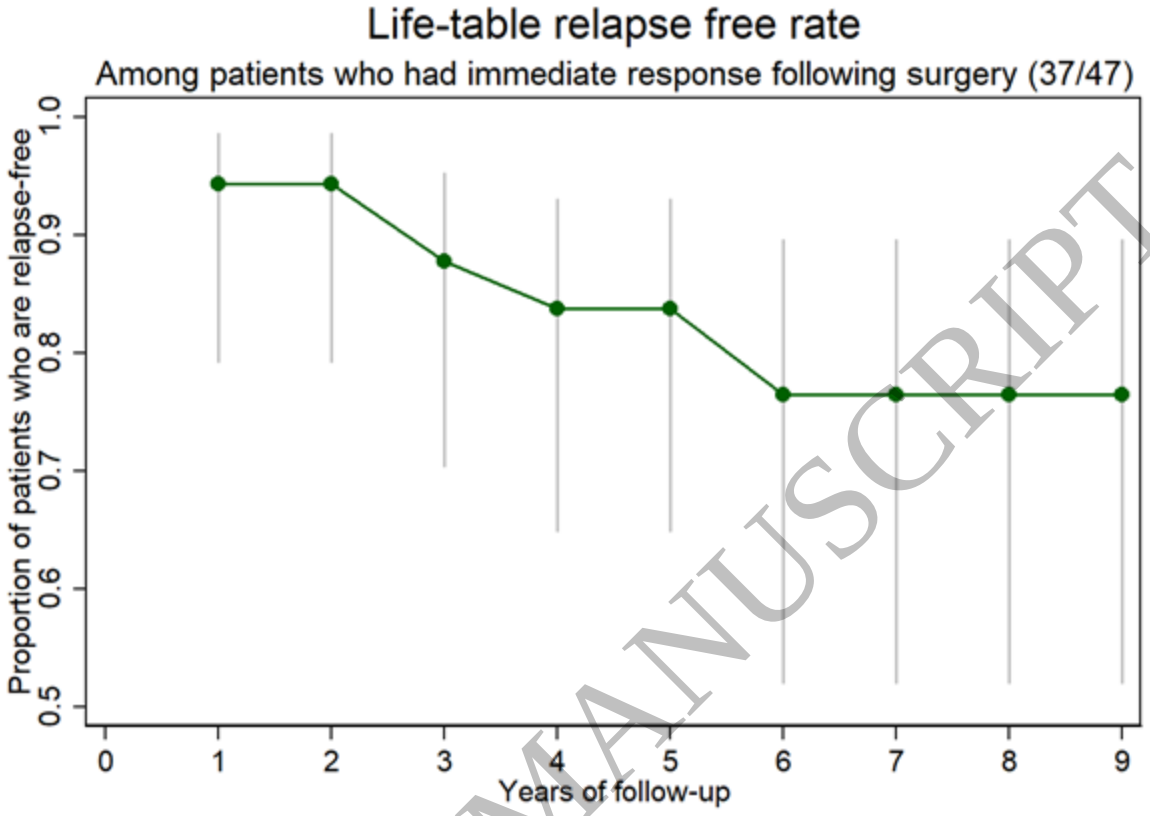

Figure 3
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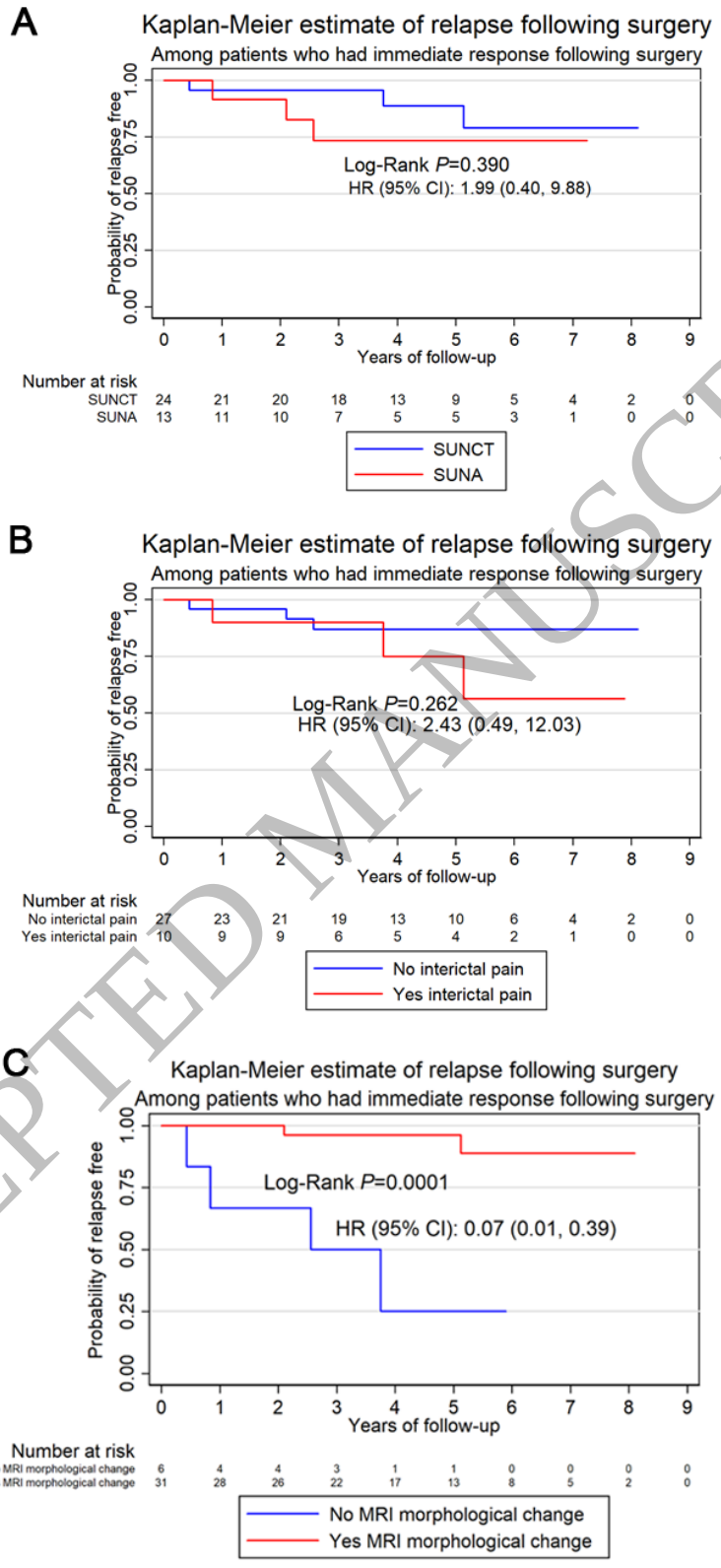

Figure 4
114x229 mm (9.1 x DPI)