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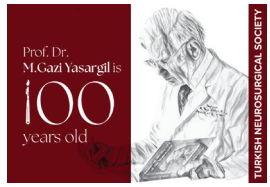

Gamma Knife Radiosurgery for Intractable Trigeminal Neuralgia - Comparative Study Between Single Versus Two Isocenter Targets

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ABSTRACT

AIM: To assess the safety and efficacy of using Two isocenter targets in Gamma Knife Radiosurgery (GKRS) for treating trigeminal neuralgia (TN) versus a single isocenter target solely at the root entry zone (REZ).

MATERIAL and METHODS: A retrospective study was conducted.The study involved 171 patients with severe facial pain caused by TN. Pain intensity was measured using a pre/post-BNI scale. Group A (85 patients) received 90 Gy using a single isocenter at REZ with a 4mm collimator, while Group B (86 patients) received 90 Gy at two isocenters of the REZ and distal cisternal segment. Statistical analyses were done to assess differences between post-BNI scores and pain-free durations in the groups.

RESULTS: Both groups had a mean patient age of 50 years. Group A had a longer presurgical pain duration (98 months) than Group B (78 months). In Group A, 33% reported pain relief to BNI class II and 67% to class III, while in Group B, 70% reported pain relief to BNI class I and 30% to BNI class II. Group A had a 40% 8-week pain relief rate, while Group B had a higher percentage of pain-free durations of 6-7 weeks (21%) and 9 weeks (39%). Group B had a higher incidence of post-op facial numbness (27% vs. 14% in Group A). Significant differences existed between post-BNI pain intensities and pain-free durations in both groups.

CONCLUSION: Patients who received 90 Gy radiation at two isocenters had better outcomes than those with a single isocenter for GKRS. While Group B experienced earlier pain relief, Group A had fewer side effects. Two-isocenter GKRS is a safe and effective alternative for TN patients with a better pain management profile but an increased risk of facial hypoesthesia.

KEYWORDS: Gamma knife radiosurgery, Trigeminal neuralgia, Isocenter, Root entry zone, Barrow Neurological Institute pain scale

INTRODUCTION

Trigeminal neuralgia (TN) is commonly referred to as "tic douloureux" and characterized by severe paroxysmal pain in the facial region innervated by the trigeminal nerve. The pain is sudden, intense, and often described as electric shock-like (4). Walter Dandy discovered that most patients suffering from this condition have an overlying blood vessel compressing the trigeminal nerve at the root entry zone (REZ), leading to pain. The superior cerebellar artery (SCA) is the most commonly involved vessel, other arteries or even veins can also contribute to this condition, although the exact etiology remains unknown (21). Multiple factors can contribute to TN, which may be idiopathic or secondary to tumor, trauma, multiple sclerosis, herpes zoster, or multiple sclerosis, resulting in secondary trigeminal neuropathy (14). Diagnosis is based on clinical history and exclusion of other diseases using MRI brain contrast. Patients with idiopathic TN are typically managed with medication, with carbamazepine as the first choice. Surgical options include microvascular decompression (MVD), radiofrequency ablation, glycerol injection, balloon compression, and radiosurgery. MVD operation is considered

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the gold standard for medically refractory TN. Surgical intervention is limited to patients who do not respond to medical management or experience intolerable pain or side effects from the therapy (7,13). However, surgical interventions carry risks of complications (3). The concept of treating trigeminal neuralgia with radiosurgery was pioneered by Lars Leksell in 1951. He attached an X-ray tube to a prototype frame (Leksell frame) with a polar arc to deliver a dose of radiation for treating TN, resulting in a successful outcome (15). Since then, several authors have reported encouraging clinical results using GKRS, considering it safe, least invasive, and preferable compared to other interventional and radiation treatments available (8-10). The long-term outcomes of GKRS treatment in TN patients have shown both safety and effectiveness, although results are not as impressive as those of MVD, which may not be suitable for all patients (20). The efficacy and safety of single-target GKRS for TN therapy has been previously demonstrated by several researchers. The conventional GKRS target is commonly chosen at the REZ (12,17,19). In this study, we report our experience of using two isocenter GKRS in comparison to a single Isocenter target in patients suffering from TN.

MATERIAL and METHODS

Study Design & Setting

A retrospective study was conducted from January 2008 to July 2022. Ethical approval was obtained from the institutional review board (IRB no: 1437/23; Date: 1st August 2023). We treated 171 patients with intractable TN using GKRS. The patients were followed for two years.

Inclusion and Exclusion Criteria

The patients included those who experienced severe facial pain due to TN refractory to medical therapy with maximum possible treatment, with no abnormality on MRI brain observed diagnosed by the team of neurosurgeon and neuro physician. Patients who underwent microvascular decompression or rhizotomy were included in this study. Patients with trigeminal neuralgia symptoms due to Brain tumors, post-surgical symptoms, or trauma related to a secondary cause were excluded.

Data Collection

Patient data was collected, including age, gender, duration of pain in months, location of pain on either the left or right side, information on previous treatment, and whether a single or two isocenter was used for target selection. Pain assessment scores from pre and post-treatment using the BNI scale were also obtained. Additionally, information on any complications and the duration of pain relief in weeks were recorded. The analysis focused on the associations between pain control status, complications, and recurrence between single and two isocenters. The BNI pain intensity score includes five classes: no trigeminal pain and no medicines required; II=occasional pain and not requiring medicines; III=some pain adequately controlled with the medicines; IV= some patient not adequately controlled with medicines and V= severe pain and no pain relief.

GKRS Single and Two Isocenters

Patients underwent neurological examinations, brain imaging, and GKRS treatment using Leksell Gamma Knife 4C or Icon models (Elekta, Stockholm, Sweden) by a team of medical experts, including a radiation oncologist, neurosurgeon, and medical physicist. The Gamma Knife team evaluated patients during routine follow-ups to assess therapy responsiveness, pain relief, and development or worsening of facial numbness. Patients were examined at 3, 6, 12, and 24 months after GKRS. Group A (85 patients) received a single isocenter dose of 90 Gy at the REZ with a 4-mm collimator, while Group B (86 patients) received 90 Gy at two isocenters of the REZ and distal cisternal segment of the TN.

Surgical Procedure

Patients who were part of the study were given moderate sedation through an IV with 1 mg midazolam. Following local anesthesia, a Leksell stereotactic headframe was attached to the patient's head, and MRI images were taken using gadolinium contrast and constructive interference in steady state (CISS) to view the affected trigeminal nerve's cisternal portion. Gamma Plan software was used to develop a treatment plan, with the radiation dose being distributed to the trigeminal nerve to ensure that the 50% isodose line was tangential to the brainstem. Group A patients had a single isocenter targeted at the trigeminal nerve REZ, while Group B patients had two isocenters targeted at the proximal and distal cisternal portion of the affected trigeminal nerve, 3 to 5mm apart and away from the brainstem surface. Both groups received a radiation dose of 90 Gy with 100 % dose to the trigeminal nerve to minimize radiation to the brainstem, with the brainstem surface not exceeding 10 to 15 Gy.

Data Analysis

Chi-square tests were applied between groups (A and B) to find the significant/insignificant differences between Gender (male/female), distribution of different nerves, side impacted (left/right), and pain-free durations. An independent samples t-test was applied to determine the significant difference between mean values of patients' ages and duration of pain as symptoms and pain relief experienced before GKS. Mann Whitney U test was applied to compare the patient groups concerning the post-BNI scores to assess pain relief in patients.

RESULTS

Background Clinical Information of Patient Groups

Table I shows the detailed background clinical information, including the prevalence and mean values of the included variables. The mean age was 50 years in both groups. Most of the patients had pain for a long duration, with median pre-surgical pain durations of 98 and 78 months in groups A and B, respectively. The proportion of male patients was higher in both groups, comprising 52/85 (61%) male and 33/85 (39%) female patients in group A and 49/86 (57%) male and 37/86 (43%) female patients in group B. The majority of patients have pain in the distribution of V2 and V3 (50.5% / 54.6%), followed

Table I: Background Clinical Information of Patients with Trigeminal Neuralgia (TN) [N=171]

Group A (single isocenter) n=85		**Group B (two isocenters) n=86**		
Variables	**Mean ± SD**	**Variables**	**Mean ± SD**	**Statistical Analysis**
Age (years)	50 ± 12.75	Age (years)	50.25 ± 13.68	t=0.123 p-value:0.901
Duration of symptoms (months)	98.47 ± 77.36	Duration of symptoms (months)	77.89 ± 68.71	t=1.83 p-value:0.067
	Prevalence n (%)		**Prevalence n (%)**	
Gender		**Gender**		
Male	52 (61.17)	Male	49 (56.97)	χ^2: 0.31 p-value: 0.57
Female	33 (38.8)	Female	37 (43.02)	
Distribution of nerve		**Distribution of nerve**		
V1+V2	9 (10.58)	V1+V2	15 (17.44)	χ^2: 2.30 p-value:0.680
V2+V3	43 (50.58)	V2+V3	47 (54.65)	
V1+V2+V3	7 (8.23)	V1+V2+V3	6 (6.87)	
V1	1 (1.17)	V1	1 (1.16)	
V2	22 (25.88)	V2	17 (19.76)	
V3	3 (3.52)	V3	0 (0)	
Left Side	30 (35.29)	Left Side	39 (45.34)	χ^2: 1.79 p-value:0.180
Right Side	55 (64.70)	Right Side	47 (54.65)	
Previous treatments		**Previous treatments**		
Medication	59 (69.41)	Medication	64 (74.41)	-
Microvascular Decompression	13 (15.29)	Microvascular Decompression	5 (5.81)	
Neurectomy	5 (5.88)	Neurectomy	3 (3.48)	
Radiofrequency ablation	1 (1.17)	Radiofrequency ablation	2 (2.32)	
Previous Gamma Knife	2 (2.35)	Glycerol Rhizotomy/Injection	2 (2.32)	
Rhizotomy	4 (4.70)	Temporomandibular joint injection	1 (1.16)	
Intraoral nerve block	1 (1.17)	Intraoral nerve block	0 (0)	
Nerve block	0 (0)	Nerve block	4 (4.65)	
Tooth extraction	0 (0)	Tooth extraction	5 (5.81)	

by V2 alone (25.8% / 19.8%) and V1 and V2 (10.5% / 17.4%) in Group A and Group B, as shown in Table I. Right-sided pain was more common, affecting 102 patients (59.6%) compared to 69 patients on the left side (40.3%). Most patients in both groups (69% in Group A and 74% in Group B) had previously been treated for TN with more than one pharmaceutical agent for pain, and forty-eight patients (28%) had previously undergone invasive procedures, as summarized in Table I.

Pre- and Post-GKRS BNI Scores in Patients' Groups

The BNI Pain scale was used to document the pain response before and after the GKRS procedure. Details about pre- and post-GKRS BNI pain scores, pain relief duration, and complications are presented in Table II. Most patients (69/85; 81%) reported class IV pre-BNI pain intensity in Group A treated with a single isocenter. However, all patients in group B (86/86;100%) had class IV and V pre-BNI pain intensities and were treated with two isocenters. Pain relief was documented at a 3-month duration after GKRS using the BNI pain score. All the patients in both groups responded to the treatment initially. The majority of patients, 57/85(67%) in Group A, achieved adequate pain control (BNI Class III), followed by 28/85(33%)

Table II: Pre and Post Barrow Neurological Institute (BNI) Scores, Pain Relief Duration, and Complications

Group A (single isocenter) n=85	**Prevalence n (%)**	**Group B (two isocenters) n=86**	**Prevalence n (%)**
Target Selection: Single Retrogasserian/REZ (root entry zone)	85 (100)	Target Selection: Two Retrogasserian/Distal Cisternal	86 (100)
Pre-op BNI Scale		**Pre-op BNI Scale**	
Class I	0 (0)	Class I	0 (0)
Class II	0 (0)	Class II	0 (0)
Class III	6 (7.05)	Class III	0 (0)
Class IV	69 (81.17)	Class IV	86 (100)
Class V	10 (11.76)	Class V	0 (0)
Post-op BNI Scale		**Post-op BNI Scale**	
Class I	0 (0)	Class I	60 (70)
Class II	28 (33)	Class II	26 (30)
Class III	57 (67.1)	Class III	0 (0)
Class IV	0 (0)	Class IV	0 (0)
Class V	0 (0)	Class V	0 (0)
Duration of Pain Relief (Weeks)		**Duration of Pain Relief (Weeks)**	
4 weeks	0 (0)	4 weeks	3 (3.48)
5 weeks	0 (0)	5 weeks	5 (5.81)
6 weeks	1 (1.17)	6 weeks	18 (20.93)
7 weeks	3 (3.52)	7 weeks	18 (20.93)
8 weeks	34 (40)	8 weeks	33 (38.72)
9 weeks	19 (22.35)	9 weeks	6 (6.97)
10 weeks	18 (21.17)	10 weeks	3 (3.48)
Chi-Square test conducted between 6-10 weeks prevalence: χ^2: 43.37, p-value<0.00001*			
11 weeks	5 (5.88)	11 weeks	0 (0)
12 weeks	5 (5.88)	12 weeks	0 (0)
Mean: 9±1.27 weeks		*Mean: 7.19 ± 1.30*	
t-test (independent samples) between mean values of pain-free durations: t=9.20; p-value<0.0001*			
Complications		**Complications**	
Nil	67 (78.82)	Nil	56 (65.11)
Facial numbness	12 (14.11)	Facial numbness	23 (26.74)
Prior Facial numbness + tearing	1 (1.17)	Prior Facial numbness + tearing	4 (4.65)
Prior Hearing loss	2 (2.35)	Prior Hearing loss	0 (0)
Prior Hearing loss + facial numbness	1 (1.17)	Prior Hearing loss + facial numbness	1 (1.16)
Prior Tearing	1 (1.17)	Prior Tearing	2 (2.32)
Prior Weakness in chewing	1 (1.17)	Prior Weakness in chewing	0 (0)

**Significant result.*

reported good pain control (BNI Class II). Whereas in group B, 60/86 (70%) were assessed to have excellent pain control (BNI Class- I), while 26/86 (30%) reported Pain alleviation to BNI Class -II (good pain control). None of the patients from both groups had treatment failure or recurrence during the initial three months after GKRS. When compared to single isocenter targets, patients treated with two isocenters significantly improved their BNI pain scores, which were consistent with pain alleviation.

Pain Relief Durations

The 8-week pain relief was observed in the majority (34/85;40%) of group A patients, followed by 9-week in 22% and 10-week in 21% of patients. About 6% of patients reported 11–12 weeks of pain relief duration in group A. The 6–7-week pain-free duration was observed in 18/86(21%) patients in group B. However, most group B patients (33/86;39%) reported a pain-free duration of 9 weeks. The other details on pain-free durations are mentioned in Table II. There existed a significant difference between pain-free durations (6-10 weeks) among the two groups (p value<0.00001). The mean pain-free duration was nine weeks in group A and seven weeks in group B (p value 0.0001), confirming early pain remission in individuals treated with two isocenters. Maintenance of Pain Relief

The data collected from the follow-up evaluations was analyzed to assess the duration of pain relief. The duration of pain relief was measured from the time it began until it fell below 40% pain relief with medication, recurred, or remained at the initial level. Group A had a mean follow-up of 18.5 months (range -3 to 24 months), and 75 patients (88%) maintained more than 50% pain relief with medication from 6 to 12 months, while 59 patients (70%) maintained it from 12 to 24 months. On the other hand, Group B had a mean follow-up of 17.8 months (range 3 to 24 months), and 84 patients maintained more than 50% pain relief with medication from 6 to 12 months. However, eight patients in Group B had poor pain control (40% pain relief with medication) at 12 to 24 months, leaving only 75 pain-free patients. Overall, 36 patients from both groups were considered to experience treatment failures due to poor pain control at the last follow-up. Patients who received treatment with two isocenters had better pain relief maintenance at the final follow-up compared to those treated with only one isocenter.

Complications

The majority of patients in both groups did not experience issues after GKRS. However, a small number reported new facial numbness and tingling sensations. In Group A, 12 patients (14%), while in Group B, 26 patients (27%) reported these symptoms. Except for two patients with bothersome numbness after treatment with two isocenters, the numbness was generally mild and did not significantly impact quality of life. There were no reports of anesthesia dolorosa or chewing problems in either group. For more information on complications, refer to Table II.

Recurrence

In Group A, 23 patients experienced the recurrence of their trigeminal pain at their original level after an average of 30 months. In contrast, only two patients in Group B had a relapse of their trigeminal pain after 24 months of follow-up.

Comparisons of post-BNI scores and pain-free durations in groups

Statistical analysis (Table III) showed that a significant difference (p value<0.00001) exists between post-BNI pain intensities in group A and group B. A significant difference (p value<0.00001) also exists between pain-free durations in both groups.

DISCUSSION

The study aimed to investigate the safety and effectiveness of using two isocenter targets for treating pain in trigeminal nerves with GKRS. Patients in Group A had a significantly longer duration of symptoms compared to Group B (98% and 77%, respectively). Patients in Group B had a significant improvement in BNI score, and those with class II and above reported complete resolution of pain. Although the duration of pain relief was the same between both groups in the eighth week, Group B showed significantly better results in the 6th and 7th weeks post-GKRS, and they maintained lower levels of pain compared to Group A. The study also found that 26% of patients in Group B developed facial numbness compared to 14% in Group A. There was a significant difference in post-BNI pain intensities between the two groups, and the pain-free duration was also significantly different. Several authors have suggested that increasing the dose of the trigeminal nerve leads to better pain control and greater benefits when using two isocenters. A 10-year study was conducted on TN patients to evaluate the effectiveness of Two-isocenter GKRS. The study revealed that patients who received this treatment experienced earlier pain relief, with a median onset of two

Table III: Comparisons of Post BNI Scores and Pain-Free Durations (in Weeks) Between Group A (Single) and Group B (Double Dose)

Mann Whitney U Test Results	Z score	U value	p-value
Comparison of Post BNI scores between: group A (single isocenter) and group B (two isocenters)	8.60	870	**<0.00001***
Comparison of pain-free duration between: group A (single isocenter) and group B (two isocenters)	7.54	1213.5	**<0.00001***

**Significant result.*

months. Furthermore, individuals with a shorter TN history and no prior surgery experienced even earlier relief from pain. The study identified only nine patients who experienced problematic facial numbness, which was linked to multi-branch involvement. Based on the study's results, it can be concluded that 2-isocenter GKRS is a safe and successful alternative for TN patients (22). However, the effectiveness of GKRS in treating TN using various radiation dosages was studied. The study found that using two isocenter dosages led to a more pronounced response. The treatment involved using a single isocenter in 27 patients and two isocenters in 36 patients to perform GKRS on the REZ of the trigeminal nerve. Initially, a 90% response rate was observed, with a 27% full response rate. Furthermore, the patients who received two isocenter dosages showed a greater improvement in their BNI scores, thus highlighting the effectiveness of this technique (1). While analyzing the effects of GKRS on 100 patients suffering from medically resistant TN, two GKRS target locations were used at the REZ and the retrogasserian portion. A single isocenter was used to administer 80-90 Gy radiation, using a 4-mm collimator. The authors found that the posterior targeting group (REZ) had better pain control and a lower complication rate than the anterior group (Retrogasserian). Fifteen of the patients experienced a recurrence of facial pain (11). The study involved treating 97 TN patients and increasing the radiation dose from 70 to 90 Gy. Among the 84 patients who were evaluated, with an average follow-up of 8.9 months, the total response rate was 70.2%, and the complete response rate was 36.9%. It was observed that patients who received treatment with two isocenters had better BNI scores at 12 months, and those who received more than 85 Gy had a longer duration of response. Minor numbness due to GKRS was reported by only 11% of the patients, and on follow-up, five of them fully recovered. Therefore, two isocenter GKRS were found to remain effective for treating TN, with improved response rates observed for doses of 85 Gy or higher. Moreover, there were no adverse effects associated with the treatment (13). In a study conducted on 117 consecutive radiosurgery patients, data on case features and outcomes were collected. Total pain relief without medication was the dependent variable for face discomfort. After an average 26-month follow-up, the rates of achieving and maintaining good results at one- and three years post-radiosurgery were 57% and 55%, respectively. Of the patients, 37% developed new chronic trigeminal impairment, with 25% experiencing tolerable numbness or paresthesia and 12% experiencing troublesome dysesthesias, which were only associated with a 90 Gy radiation dosage. The study established a link between pain reduction following GKRS and new face sensory loss. While MVD is preferred for medically fit TN patients due to the uncertain long-term outcomes of radiosurgery, GKRS remains a safe and effective treatment option with promising initial outcomes (16).

There is considerable debate surrounding the diminishing pain relief post-GKRS for TN. This study examined the anatomical and radiosurgical characteristics of patients who received an average radiation dose of 80 Gy. It observed that pain relief declined more rapidly in patients where a small portion of the nerve (35%) received over 80% of the maximum dose, particularly when the shot was within 8 mm of the pons. Enhancing the effectiveness of GKRS necessitates a tailored approach, accounting for the unique anatomical and radiosurgical features of each patient (2). Long-term outcomes of GKRS in treating medically intractable trigeminal neuralgia (TN) in 36 patients were reported. The study followed patients for a minimum of 36 months and administered a median radiation dosage of 45 Gy to the affected trigeminal nerve through a 4-mm isocenter. The study found that the rate of early pain reduction was significant, with 80.5% of patients experiencing relief in an average of 1.6 months after therapy. At the three-year mark, 67% of patients were pain-free (BNI I), and 75% had a favorable treatment result. However, 11% of patients reported bothersome facial numbness after treatment. The study also suggests that individuals over the age of 70 may be excellent candidates for radiosurgery (6).

After undergoing GKRS for TN, some patients may not experience pain relief or may have a recurrence of pain. In the following study, they shared their findings on the efficacy of repeat GKRS treatments for TN in 30 patients who had undergone three or more GKRS treatments. The study showed that the outcomes of the third treatment were similar to the first two treatments in terms of long-term pain relief, recurrence, and adverse effects. However, it took longer for pain relief to occur after the third treatment, and 29% of patients experienced new or worsening facial sensory dysfunction. Over a median follow-up period of 39 months, 77% of patients continued to experience complete or partial pain relief (5). The efficacy of GKRS for TN was evaluated by targeting the trigeminal ganglion (TG) and adjacent nerve fibers. Thirty TN patients underwent GKRS treatment, resulting in pain relief within an average of 7 days for the majority of patients (93.3%). Multivariate analysis indicated that approximately 70% of patients would remain pain-free for up to 40 months. With an 86.6% success rate and minimal side effects, GKRS is a viable option for TN treatment (20). During a 10-year follow-up period, the lasting efficacy of GKRS for essential TN was investigated in 103 patients. Pain assessment was conducted using the BNI pain intensity scale, while complications were evaluated using the BNI numbness scale. The results revealed favorable therapeutic effects of GKRS and spontaneous resolution of severe complications. Consequently, the researchers suggest expanding the eligibility criteria to encompass patients who express a strong desire for this therapy (18).

Limitations

The study lacks a comparison with MVD operation or the outcomes achieved with other technologies such as CyberKnife. Conducting a multicenter randomized controlled study would provide more definitive conclusions. Furthermore, two-isocenter GKRS may lead to prolonged numbness as compared to single-isocenter.

CONCLUSION

GKRS emerges as a promising treatment for TN patients. Two Isocenters GKRS, employing a 90 Gy radiation dose, has

demonstrated superior efficacy in alleviating trigeminal nerve symptoms compared to single Isocenter GKRS, despite the latter exhibiting a more favorable side effect profile. Patients receiving Two Isocenters therapy experienced earlier and longer-lasting pain relief. Overall, the favorable therapeutic benefits of GKRS for TN suggest its potential applicability for individuals favoring this treatment approach. However, careful consideration of potential adverse effects and long-term consequences is crucial in treatment decision-making. Therefore, extensive longitudinal studies are necessary, and further research efforts may provide insights into the long-term efficacy of this treatment option.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: KA, AK

Data collection: ZS, KA

Analysis and interpretation of results: KA

Draft manuscript preparation: KA, AK, ASMH

Critical revision of the article: ASMH, AK

Other (study supervision, fundings, materials, etc...): KA, AK, ZS, ASMH

All authors (KA, AK, ZS, ASMH) reviewed the results and approved the final version of the manuscript.

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