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Original Article

Frameless image-guided linear accelerator (LINAC) stereotactic radiosurgery for medically refractory trigeminal neuralgia: Clinical outcomes in 116 patients

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Received: 11 February 2024
Accepted: 04 May 2024
Published: 31 May 2024

DOI
10.25259/SNI_101_2024

Quick Response Code:

ABSTRACT

Background: Frameless image-guided radiosurgery (IGRS) is an effective and non-invasive method of treating patients who are unresponsive to medical management for trigeminal neuralgia (TN). This study evaluated the use of frameless IGRS to treat patients with medically refractory TN.

Methods: We performed a retrospective review of records of 116 patients diagnosed with TN who underwent frameless IGRS using a linear accelerator (LINAC) over 10 years (March 2012-February 2023). All patients had failed medical management for TN. Facial pain was graded using the Barrow Neurological Institute (BNI) scoring system. Each patient received a BNI score before frameless IGRS and following treatment. Failure was defined as a BNI score IV-V at the last follow-up and/or undergoing a salvage procedure following IGRS.

Results: All patients had a BNI score of either IV or V before the frameless IGRS. The mean follow-up duration for all 116 patients following IGRS was 44.1 months. Most patients (81 [69.8%]) had not undergone surgery (microvascular decompression [MVD] or rhizotomy) or stereotactic radiosurgery (SRS) for TN before frameless IGRS. A total of 41 (35.3%) patients underwent a salvage procedure (MVD, rhizotomy, or an additional IGRS) following frameless IGRS. The mean duration between the initial frameless IGRS and salvage procedure was 20.1 months. At the last follow-up, a total of 110 (94.8%) patients had a BNI score of I-III. No complications were reported after the frameless IGRS. The BNI score at the last follow-up was lower compared to the initial BNI for patients regardless of prior intervention ($P < 0.001$). Patients who failed IGRS had a higher BNI score at the last follow-up compared to those who did not fail IGRS (2.8 vs. 2.5, $P = 0.05$). Patients with pain relief had a shorter follow-up compared to those with pain refractory to SRS (38.0 vs. 55.1, $P = 0.005$).

Conclusion: In this large cohort of patients with medically refractory TN, frameless IGRS resulted in durable pain control in the majority of patients without any toxicity.

Keywords: Linear accelerator, Neurology, Radiation Oncology, Stereotactic radiation, Trigeminal neuralgia

INTRODUCTION

According to the Beta version of the 3rd edition of the International Classification of Headache Disorders 3 Beta, trigeminal neuralgia (TN) is a debilitating condition marked by recurrent

unilateral brief electric shock-like pain paroxysms that are abrupt in onset and termination.[11] Affecting one or more divisions of the trigeminal nerve, TN may be triggered by innocuous sensory stimuli such as teeth brushing or touching the face.[7,19] The excruciating pain may significantly decrease one's quality of life.[33] TN is classified as (1) classical due to morphologic changes in the trigeminal nerve root from vascular compression, (2) secondary due to an identifiable underlying neurologic disease (tumor at the cerebellopontine angle or multiple sclerosis), or (3) idiopathic.[7,10,19] The pathophysiology involves demyelination of primary sensory trigeminal afferents in the root entry zone (REZ) caused by an enlarged blood vessel (usually the cerebellar artery) pressing against the trigeminal nerve.[19,22] The incidence rates of TN in the United States range between 5.9 and 12.6/100,000 individuals with a lifetime prevalence of 0.7/1000 people.[22,33] TN is more common in individuals >50 years and affects females more often than males.[10,19] It is most frequent in the 2nd division, followed by the 3rd division of the trigeminal nerve, is usually ipsilateral, and occurs more often on the right side of the face.

TN is classified into primary TN, which includes typical type 1 TN (predominantly paroxysmal pain) and atypical type 2 TN (predominantly constant pain), as well as secondary TN.[13] Type 2 TN is often associated with worse outcomes following stereotactic radiosurgery (SRS).[3,13,20,30] In Marshall *et al*.' study of outcomes comparing type 1 and type 2 TN following gamma knife radiosurgery, patients with type 2 TN had decreased initial response rates after SRS and decreased durability of pain relief.[20]

Patients with TN are initially medically managed with sodium channel blockers (carbamazepine and oxcarbazepine); other medications (lamotrigine, baclofen, pregabalin, and gabapentin) may be subsequently added to the regimen.[19,33] For medically refractory patients, surgical treatments such as microvascular decompression (MVD) or rhizotomy may prove advantageous.[1,19] SRS, a less invasive procedure that lacks the surgical risks of MVD (facial numbness/palsy, cerebrospinal fluid leaks, hearing deficits, and incisional infections), may be offered to older patients who are poor surgical candidates due to comorbidities.[10,17,19,24] When evaluated retrospectively, MVD has been reported to be superior to SRS with a significantly higher health-related quality of life, higher initial cure rate, lower rate of recurrence and complications, complete pain relief, durability of response, and preservation of trigeminal sensation.[17,33] However, most patients who undergo SRS are either not candidates for MVD or have recurrent pain after MVD, usually several years later. Pain relief from SRS is related to the radiation dose delivered to the postganglionic intracranial nerve, with increased rates of pain relief with higher doses (usually between 80 and 90 Gy).[14,21] While this range represents the optimal dose, it may not be possible due to brainstem toxicity and postprocedural trigeminal nerve dysfunction.[14] A wide range (22–94%) in rates of pain-free outcomes is associated with SRS.[22] For those patients who continue to experience symptoms following SRS, salvage procedures such as surgery (MVD, rhizotomy) or additional SRS treatments may be pursued.[2]

The Barrow Neurological Institute (BNI) scoring system classifies TN based on levels of pain and medication requirements (I: No pain, no medication; II: Occasional pain, not requiring medication; III: Some pain, adequately controlled with medication; IV: Some pain, not adequately controlled with medication; and V: Severe pain/no pain relief).[25] Comparing the BNI score before SRS and post-SRS may offer significant insight into the effectiveness of treatment.

In our previous study of 20 patients who underwent frameless image-guided radiosurgery (IGRS) for refractory TN,[26] we demonstrated that this technique was an effective and noninvasive method of treating older individuals who were unresponsive to medical management. In addition to the small slice thickness of 0.6 mm that provided increased resolution at the target, mapping of the patient's movement during treatment confirmed the benefit of using IGRS.

Herein, we expand on our previous study by greatly increasing the number of patients with medically refractory TN who were treated with frameless IGRS and following their post-IGRS course over a longer duration of time. The benefits and limitations of various modalities of SRS, as well as percutaneous procedures for TN before frameless IGRS, are discussed. We have also compared the clinical characteristics and treatment outcomes between patients diagnosed with type 1 and type 2 TN. The challenges of treating patients with concurrent multiple sclerosis and TN are also highlighted.

MATERIALS AND METHODS

Under an Institutional Review Board-approved protocol and according to the Declaration of Helsinki, we performed a 10-year (March 01, 2012–February 28, 2023) retrospective review of consecutively treated patients with TN who underwent frameless IGRS using the LINAC. All patients had failed medical management for TN. All patients were evaluated by a neurosurgeon, neurologist, and radiation oncologist. Each patient received a BNI score before the frameless IGRS and following treatment.

Frameless IGRS failure was defined as receiving a BNI score of IV or V at the last follow-up and/or undergoing a salvage procedure for TN (MVD, rhizotomy, or additional frameless IGRS) after the initial frameless IGRS. Good-to-excellent results were defined as a BNI score of I-III.

Simulation and treatment delivery

The immobilization, simulation, treatment planning, and SRS delivery methodology were previously published.[26] Patients

were treated with 80, 85, or 90 Gy with a mode of 85 Gy. The dose was prescribed to a point in the trigeminal nerve so that at least the 60–80% isodose line encompassed the nerve. Briefly, patients were simulated in the head-first position with a three-layer thermoplastic mask. A 40-slice Siemens computed tomography (CT) simulator obtained a 0.6 mm spacing axial electron density map that was fused to a 0.5 mm constructive interference in a steady state (CISS) T2 brain magnetic resonance imaging (MRI). A seven to nine non-coplanar arc plan spanning 60–140° was generated to deliver the prescription dose to a point along the trigeminal nerve as determined by the neurosurgeon and radiation oncologist. The linear accelerator imaging to treatment isocenter was verified to be less than 0.5 mm in three dimensions before each procedure. SRS was delivered after the thermoplastic mask was applied with the patient position monitored constantly in real-time using both optical surface tracking coupled with intermittent orthogonal X-ray detection. This allowed correction of patient positioning before each arc or patient motion was detected, resulting in translational accuracy within 0.5 mm and rotational accuracy within 1°. Postprocedure MRI brain with gadolinium done 6 months later verified lesioning of the target.

After each patient signed informed consent, a bivalve-style thermoplastic mask was fabricated to immobilize the head. All patients were simulated and treated supine and head-first. Next, a stereotactic localizer frame was attached to the imaging frame, and then, patients underwent a 0.6 mm axial slice CT scan using a 40-slice Siemens Sensation Open (Siemens, Munich, Germany) from the vertex to the third cervical vertebra. We obtained a 0.5 mm CISS T2 MRI sequence using a three Tesla magnet with zero gantry tilt and registered the CT and MRI datasets using BrainLAB iPlan RT Image software.

Treatment planning

The affected side trigeminal nerve and organs at risk were contoured by the neurosurgeon and radiation oncologist on the fused data set. There was a 0 mm expansion from the prescription point to the planning target volume. The trigeminal nerve and brainstem were contoured on a T2 CISS sequence with 0.6 mm slice spacing. The use of real time orthogonal imaging allows for no expansion to minimize dose to the brainstem. The isocenter was placed along the trigeminal nerve, proximal to any vascular abnormality or nerve compression. The SRS plan was prescribed at the isocenter, and all plans used between seven and nine non-coplanar arcs with fixed diameter cones ranging from 4.0 to 7.5 mm aperture, with total scatter factors of 0.669 and 0.815, respectively [Figure 1]. Each arc used between 60 and 140°. For dose calculations, the grid resolution was 0.5 mm. The mean maximum brainstem dose was 28.9 Gy with a standard deviation of 13.2 Gy, the mean dose to 0.1 cc of the brainstem was 8.3 ± 2.9 Gy, and the mean dose to 1 cc of the brainstem was 3.2 ± 2.8 Gy.

Evaluation after the IGRS

Patients were seen 1 month after the frameless IGRS and every 2–3 months afterward. Patients continued to follow up until they were pain-free and all TN medications were discontinued. Facial sensation was assessed, and a BNI score was determined.

Statistical analysis

We employed descriptive statistics for data summarization. Continuous measures were presented as mean ± standard deviation or median with interquartile range, while categorical data were expressed in frequencies and percentages. The relationship between categorical variables was assessed using Chi-square or Fisher's exact tests, and continuous variables were compared using *t*-tests or Mann–Whitney U-tests, as dictated by the data distribution. Survival outcomes were estimated with the Kaplan–Meier method, with the Log-Rank test assessing group differences. A Cox proportional hazards model was used to evaluate the impact of type 1 versus type 2 classification on the probability of success over time, controlling for age as a confounder. Statistical significance was predetermined at $P < 0.05$. Analyses were conducted using R software (version 4.3.1).[23]

RESULTS

Clinical characteristics

A total of 116 patients were identified with medically intractable TN who underwent frameless IGRS. The median age was 65.3 years, and the majority (68.1%) of patients were female. The clinical characteristics of patients with TN are presented in Table 1. Eleven (9.5%) patients were diagnosed with multiple sclerosis. The 2nd division of the trigeminal nerve was the most common location of symptoms (85.3% of patients).

Surgical/SRS intervention for TN before frameless IGRS

A total of 35 (30.2%) patients underwent a prior intervention for TN before the frameless IGRS [Table 1]. Of these 35 patients, 26 (74.3%) underwent only a previous surgical procedure for TN, 4 (11.4%) had only a previous SRS procedure, and 5 (14.3%) underwent both a previous surgery and SRS for TN. The prior surgeries included an MVD in 24 patients, a percutaneous rhizotomy in 10, and radiofrequency lesioning in 2. Ten patients underwent two or more previous procedural treatments. Symptoms affecting the 3rd division of the trigeminal nerve were more frequent in patients who underwent prior interventions for TN (71% vs. 58%, $P = 0.026$).

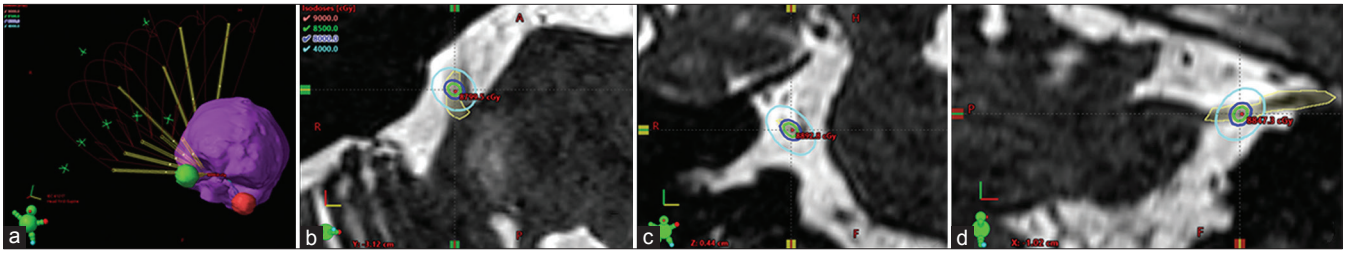

Figure 1: (a) Stereotactic radiosurgery plan with dorsal root entry zone for a patient with right-sided trigeminal neuralgia utilizing nine non-coplanar arcs with the patient position shown in the lower left corner green anthropomorphic figure. The resulting delivered dose is displayed in the (b) axial, (c) coronal, and (d) sagittal planes, with the trigeminal nerve contoured in yellow. The 40 Gy line is light blue, the 80 Gy line is dark blue, the 85% Gy line is green, and the isocenter location is red.

Table 1: Characteristics of patients who underwent a prior intervention for trigeminal neuralgia before the frameless image-guided SRS at our institution.

Characteristics	Overall (*n*=116)	No prior intervention (*n*=81)	Prior surgery (MVD/ rhizotomy) or SRS (*n*=35)	*P*-value
Gender=Male	37 (31.9)	24 (29.6)	13 (37.1)	0.516
Age (years)	65.3 (13.7)	65.4 (13.7)	65.1 (14.0)	0.907
Ever smoker=Yes	61 (52.6)	46 (56.8)	15 (42.9)	0.224
Hypertension=Yes	65 (56.0)	49 (60.5)	16 (45.7)	0.158
Hyperlipidemia=Yes	53 (45.7)	39 (48.1)	14 (40.0)	0.543
Diabetes mellitus=Yes	15 (12.9)	12 (14.8)	3 (8.6)	0.548
Multiple sclerosis=Yes	11 (9.5)	8 (9.9)	3 (8.6)	1.000
Body mass index	29.4 (7.3)	29.8 (7.2)	28.6 (7.6)	0.436
BNI score before frameless IGRS	4.3 (0.6)	4.3 (0.6)	4.3 (0.6)	0.676
Symptom laterality=Right	69 (59.5)	50 (61.7)	19 (54.3)	0.538
Division of trigeminal nerve	-	-	-	-
VI=Yes	38 (32.8)	29 (35.8)	9 (25.7)	0.389
V2=Yes	99 (85.3)	69 (85.2)	30 (85.7)	1.000
V3=Yes	64 (55.2)	39 (48.1)	25 (71.4)	0.026
Radiation dose to target (Gy)	85.6 (2.3)	85.6 (2.3)	85.7 (2.5)	0.838
1st frameless IGRS target=Meckel's	79 (68.1)	53 (65.4)	26 (71.4)	0.392
Salvage procedure	-	-	-	**0.026**
None	75 (64.7)	50 (61.7)	25 (71.4)	
SRS	13 (11.2)	12 (14.8)	1 (2.9)	
Surgery	22 (19.0)	14 (17.3)	8 (22.9)	
Surgery and SRS	6 (5.2)	5 (6.2)	1 (2.9)	
Duration between 1st frameless IGRS and salvage procedure (months)	20.1 (18.3)	21.6 (19.3)	15.9 (15.2)	0.407
Number of salvage procedures	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.269
2nd frameless IGRS=Yes	18 (15.5)	16 (19.8)	2 (5.7)	0.091
2nd frameless IGRS target=Meckel's	12 (70.6)	11 (68.8)	1 (100.0)	1.000
BNI score at last follow-up	2.6 (0.9)	2.5 (1.0)	2.8 (0.6)	0.060
Duration between 1st frameless IGRS to last follow-up (months)	44.1 (32.2)	42.1 (31.2)	48.9 (34.5)	0.299
Failure of 1st frameless IGRS=Yes	44 (38.3)	34 (42.5)	10 (28.6)	0.211

MVD: Microvascular decompression, IGRS: Image-guided radiosurgery, SRS: Stereotactic radiosurgery, BNI: Barrow Neurological Institute. Table 1. Distribution of V3 location in patients with and without prior interventions. This table presents a comparative analysis of the occurrence of V3 location in patients with prior interventions versus those without. It includes counts and percentages for nominal variables and means and standard deviations for ordinal variables. Statistical significance was assessed using Fisher's exact tests and *t*-tests, with *P*-value indicating the difference between the two groups. The value in bold indicates statistical significance.

Initial frameless IGRS

All 116 patients underwent frameless IGRS, with a mean radiation dose to the target of 85.6 Gy [Table 2]. Meckel's cave was the radiation target in 79 (68.1%) patients during the initial frameless IGRS; the dorsal REZ was the target in 37 (31.9%) patients. Observed complications and side effects were minimal or managed with medication. Fatigue, defined as increased sleeping by patients and families,

Table 2: Characteristics of patients with trigeminal neuralgia who failed frameless image-guided SRS at our institution.

Characteristics	Overall (*n*=115)	Did not fail frameless IGRS (*n*=71)	Failed frameless IGRS (*n*=44)	*P*-value
Gender=Male	37 (31.9)	24 (33.8)	12 (27.3)	0.538
Age (years)	65.3 (13.7)	65.6 (13.3)	64.8 (14.7)	0.766
Ever smoker=Yes	61 (52.6)	36 (50.7)	24 (54.5)	0.706
Hypertension=Yes	65 (56.0)	35 (49.3)	29 (65.9)	0.087
Hyperlipidemia=Yes	53 (45.7)	34 (47.9)	19 (43.2)	0.702
Diabetes mellitus=Yes	15 (12.9)	10 (14.1)	5 (11.4	0.781
Multiple sclerosis=Yes	11 (9.5)	5 (7.0)	6 (13.6)	0.330
Body mass index	29.4 (7.3)	29.0 (7.7)	29.9 (6.7)	0.506
BNI score before frameless IGRS	4.3 (0.6)	4.2 (0.6)	4.4 (0.7)	0.208
Symptom laterality=Right	69 (59.5)	41 (57.7)	27 (61.4)	0.845
Division of trigeminal nerve	-	-	-	-
VI=yes	38 (32.8)	23 (32.4)	15 (34.1)	1.000
V2=yes	99 (85.3)	61 (85.9)	37 (84.1)	0.793
V3=Yes	64 (55.2)	37 (52.1)	26 (59.1)	0.564
Prior intervention (surgery/SRS)=Yes	35 (30.2)	25 (35.2)	10 (22.7)	0.211
Radiation dose to target (Gy)	85.6 (2.3)	85.8 (2.5)	85.3 (2.0)	0.330
1st frameless IGRS target=Meckel's cave	79 (68.1)	49 (69.0)	29 (65.9)	0.838
Salvage procedure	-	-	-	**<0.001**
None	75 (64.7)	71 (100.0)	3 (6.8)	
SRS	13 (11.2)	0 (0.0)	13 (29.5)	
Surgery	22 (19.0)	0 (0.0)	22 (50.0)	
Surgery and SRS	6 (5.2)	0 (0.0)	6 (13.6)	
Duration between 1st frameless IGRS and salvage procedure (months)	20.1 (18.3)	-	20.1 (18.3)	-
Number of salvage procedures	1.2 (0.7)	-	1.2 (0.7)	-
2nd frameless IGRS=Yes	18 (40.9)	-	18 (40.9)	-
2nd frameless IGRS target=Meckel's cave	12 (70.6)	-	12 (70.6)	-
BNI score at last follow-up	2.6 (0.9)	2.5 (0.9)	2.8 (1.0)	0.052
Duration between 1st frameless IGRS to last follow-up (months)	44.1 (32.2)	38.0 (30.0)	55.1 (32.9)	**0.005**

IGRS: Image-guided radiosurgery, SRS: Stereotactic radiosurgery, BNI: Barrow Neurological Institute. Table 2. Comparison of Barrow Neurological Institute scores and time from first stereotactic radiosurgery to last follow-up between treatment failure groups. This table provides a detailed breakdown of the Barrow Neurological Institute scores at the last follow-up and the time elapsed from the first stereotactic radiosurgery to the last follow-up for patients categorized into "No Fail" and "Fail" treatment groups. It includes counts and percentages for nominal variables and means and standard deviations for ordinal variables. Statistical significance was assessed using Fisher's exact tests and *t*-tests, with *P* value indicating the difference between the two groups. The values in bold indicate statistical significance.

occurred after 42 SRS procedures, lasting from 1 to 3 weeks. A pain flare lasting 2–7 days occurred in five patients requiring dexamethasone 4 mg once daily for 4 days. Given the reported rate of 0–11% for symptomatic sensory deficits [18,29] and the number of procedures in our study, we would likely see at least one instance of clinically relevant TN dysfunction as our experience grows. Dry eye was observed in two patients, in accordance with the majority of studies, which report a 0% rate of dry eye or keratitis.[29] Physical examination performed by the neurosurgeon after frameless IGRS detected no new sensation or motor abnormalities.

Salvage procedure following initial frameless IGRS

Of the total 116 patients who underwent initial frameless IGRS, 44 (37.9%) patients failed this procedure (BNI 4–5 at last follow-up and/or undergoing a salvage procedure). A total of 41 (35.3%) patients underwent a salvage procedure following the frameless IGRS. Twenty-two (19.0%) patients underwent surgical intervention, 13 (11.2%) had a second frameless IGRS, and 6 (5.2%) had both surgery and a second frameless IGRS. Salvage surgical procedures included an MVD in 15 patients and a rhizotomy in 15 patients. A cranial nerve stimulator for the 2nd and 3rd divisions of the trigeminal nerve was placed in one patient. A total of 18 patients had a salvage frameless IGRS. The duration between the initial frameless IGRS and salvage procedure was 20.1 months. Of the 19 patients who had salvage frameless IGRS, 12 (70.6%) had their radiation targeted to Meckel's cave. One patient underwent two salvage IGRS procedures.

None of the clinical characteristics were statistically significant between the patients who failed the initial frameless IGRS and those who did not [Table 2].

BNI score at last follow-up

The mean duration between the initial frameless IGRS and the last follow-up for all 116 patients was 44.1 months. The mean BNI score at the last follow-up for all patients was 2.6. At the last follow-up, a total of 110 (94.8%) patients had a BNI score of I-III, specifically, 29 (26.4%) with an excellent response (BNI I [28 patients] or BNI II [1 patient]) and 81 (73.6%) with a good response (BNI III). Six patients (5.2%) had a BNI score of IV or V. The BNI score at the last follow-up differed between the patients who did not fail frameless IGRS and those who did fail (2.5 vs. 2.8, $P = 0.052$). Although the median values were equal between the patients who failed and did not fail treatment, the distributions, as seen in the first quartile in the patients who did not fail treatment, were significantly lower than those who did fail treatment. The time duration from the initial frameless IGRS to the last follow-up also differed between patients with pain relief from IGRS versus those who did not have relief (38.0 months vs. 55.1 months, $P = 0.005$).

The BNI score at last follow-up was lower than the BNI score before the initial frameless IGRS for patients who had a surgical/SRS intervention before the initial frameless SRS (before the initial frameless IGRS: 4.3, last follow-up: 2.8, $P < 0.001$) as well as for patients who did not have a surgical/SRS intervention before the initial frameless SRS (before the initial frameless IGRS: 4.3, last follow-up: 2.5, $P < 0.001$). The time to treatment failure was marginally ($P = 0.06$) shorter for the patients who did not have a prior intervention [Figure 2].

Clinical characteristics and treatment outcomes between patients with type 1 and type 2 TN

Of the total 116 patients with TN, 79 (68%) were diagnosed with type 1 and 37 (32%) with type 2 [Table 3]. Type 1 patients were older on average (67.9 ± 13.2 years) than type 2 patients (59.6 ± 13.3 years; $P = 0.002$) [Table 3]. Male representation was higher in the type 1 group (34.2% vs. 27.0% in Type 2), though this was not statistically significant ($P = 0.578$). Hypertension was more prevalent in type 1 patients (63.3% vs. 40.5% in type 2; $P = 0.036$). No significant differences were detected in the incidence of hyperlipidemia, diabetes mellitus, or multiple sclerosis. Similarly, body mass index was comparable across groups ($P = 0.523$). There were no significant disparities in the history of surgical or radiosurgical treatments between groups. The time elapsed from initial radiosurgery to the last follow-up was longer for type 1, although not reaching statistical significance (22.3 ± 18.8 months vs. 13.1 ± 15.3 months; $P = 0.190$). At the last follow-up, median BNI scores were equivalent between groups. Dosages to the target region and the maximum dose to the brainstem were statistically indistinguishable. The response to frameless IGRS did not differ significantly between types.

Kaplan–Meier survival estimates depicted the temporal probability of treatment success for both TN subtypes [Figure 3]. The Log Rank Test unveiled a marginally significant distinction ($P = 0.065$), suggesting a tendency for improved outcomes in type I patients. Moreover, after adjusting for age, Cox-proportional hazard regression identified a 73% increase in the probability of success for type I (HR = 1.73 [95% Confidence interval: 1.02, 2.90], $P = 0.040$).

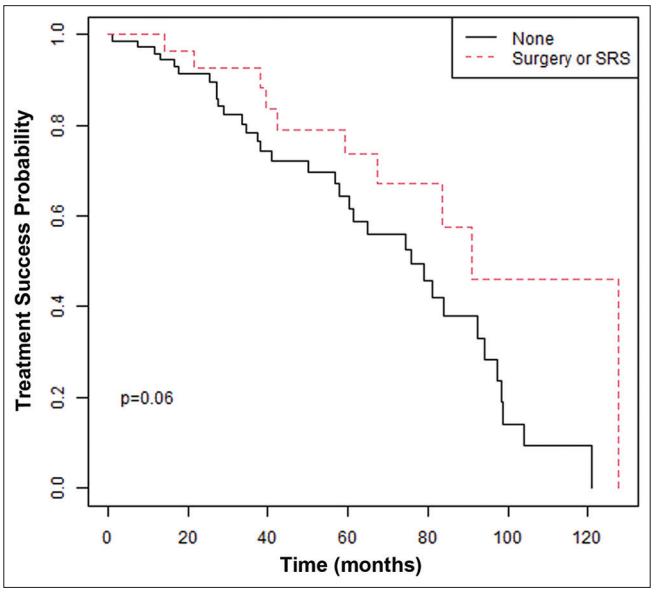

Figure 2: Kaplan–Meier plot depicting that the time to treatment failure (Barrow Neurological Institute score IV-V at last follow-up or salvage procedure) following frameless image-guided radiosurgery (IGRS) was marginally ($P = 0.06$) shorter for the patients who did not have an intervention (microvascular decompression, rhizotomy, and/or stereotactic radiosurgery) before the frameless IGRS.

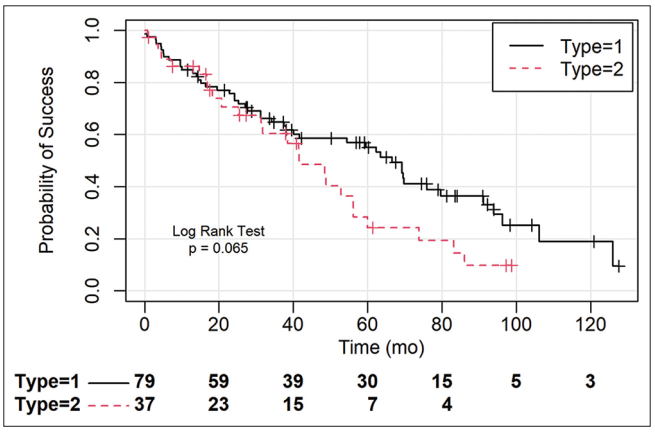

Figure 3: Kaplan–Meier survival curves comparing treatment success in type 1 and type 2 trigeminal neuralgia. This figure illustrates the estimated survival functions for both patient groups over 120 months, with the solid line depicting type 1 and the dashed line depicting type 2. A marginally significant $P = 0.065$ from the log-rank test suggests a trend toward improved survival for type 1.

Table 3: Demographic and clinical characteristics of patients with type 1 and type 2 trigeminal neuralgia.

Characteristics	Overall	Type 1	Type 2	*P*-value
	n=116	*n*=79	*n*=37	
Male (%)	37 (31.9)	27 (34.2)	10 (27.0)	0.578
Age	65.3 (13.7)	67.9 (13.2)	59.6 (13.3)	**0.002**
Ever smoker (%)	61 (52.6)	41 (51.9)	20 (54.1)	0.986
HTN (%)	65 (56.0)	50 (63.3)	15 (40.5)	**0.036**
Hyperlipidemia (%)	53 (45.7)	37 (46.8)	16 (43.2)	0.871
DM (%)	15 (12.9)	13 (16.5)	2 (5.4)	0.175
MS (%)	11 (9.5)	5 (6.3)	6 (16.2)	0.176
BMI	29.4 (7.3)	29.1 (6.7)	30.0 (8.4)	0.523
BNI initial	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	0.128
Laterality=Right (%)	69 (59.5)	47 (59.5)	22 (59.5)	1.000
Distribution (V1) (%)	38 (32.8)	30 (38.0)	8 (21.6)	0.124
Distribution (V2) (%)	99 (85.3)	66 (83.5)	33 (89.2)	0.603
Distribution (V3) (%)	64 (55.2)	41 (51.9)	23 (62.2)	0.403
Prior surgical or SRS treatment (%)	36 (31.0)	28 (35.4)	8 (21.6)	0.199
1st SRS Location=Meckel's (%)	114 (98.3)	78 (98.7)	36 (97.3)	1.000
Elapsed time (months)	20.1 (18.3)	22.3 (18.8)	13.1 (15.3)	0.190
Salvage procedure (%)	41 (35.3)	32 (40.5)	9 (24.3)	0.136
Number of salvage procedures	1.3 (0.7)	1.3 (0.7)	1.6 (0.5)	0.382
2nd SRS (%)	18 (15.5)	16 (20.3)	2 (5.4)	0.075
2nd SRS location=Meckel's (%)	12 (70.6)	10 (66.7	2 (100.0	0.884
3rd SRS (%)	1 (0.9	1 (1.3	0 (0.0)	1.000
3rd SRS location=brainstem (%)	1 (100.0)	1 (100.0)	0 (NA)	NA
BNI at last follow-up	3.0 (3.0, 3.0)	3.0 (1.5, 3.0)	3.0 (3.0, 3.0)	0.242
Dose to target (Gy)	8500 (8500, 8500)	8500 (8500, 8500)	8500 (8500, 9000)	0.056
Brainstem D1cc (Gy)	3.6 (4.8)	3.5 (4.7)	3.8 (5.0)	0.762
Brainstem D01.cc (Gy)	8.1 (2.9)	8.1 (3.1)	8.1 (2.7)	0.997
Maximum Brainstem Dose (Gy)	28.5 (13.1)	27.0 (12.0)	31.2 (14.6)	0.137
Interval from SRS to last follow-up (months)	38.0 (16.7, 68.0)	39.6 (20.5, 72.2)	31.3 (16.4, 52.9)	0.090
BNI ≥4 (%)	6 (5.2)	2 (2.5)	4 (10.8)	0.154
IGRS=Failed (%)	44 (37.9)	32 (40.5)	12 (32.4)	0.529

HTN: Hypertension, BMI: Body mass index, DM: Diabetes mellitus, MS: Multiple sclerosis, IGRS: Image-guided radiosurgery, SRS: Stereotactic radiosurgery, BNI: Barrow Neurological Institute, NA: Not applicable. Table 3. This table summarizes the key demographic factors, prevalence of comorbid conditions, and treatment-related variables within the study cohort comparing type 1 (*n*=79) and type 2 (*n*=37) TN. Statistical significance is noted in bold where applicable. The values in bold indicate statistical significance.

DISCUSSION

SRS is a viable option for patients who do not attain durable pain relief from medications or who do not want or are not candidates for invasive surgery.[22] Gamma Knife,[2,25,29] CyberKnife,[5,6,29] and LINAC[4,5,8-10,14,24,26,29] are several modalities of SRS that are tolerable and efficacious for treating medically resistant TN. Leksell introduced the stereotactic method in 1951[16] and subsequently reported its use for patients with TN in 1971.[15] SRS was initially delivered to patients using a rigid head fixation through a bolted invasive device.[5,9,12,15,16] The frameless SRS system received a U.S. patent in 1995 and was clinically introduced in 1997.[27,32] The frameless SRS, comprised of a thermoplastic mask fitted to each patient, offers more patient comfort with minimal toxicities and without incisions or anesthesia.[9,12,14,28] The frameless LINAC SRS technique has been increasingly employed in the setting of medically recalcitrant TN.[4,5,8-10,14,24,26] In Tuleasca *et al*.'s systematic review of 65 eligible studies (6461 patients) between 1951 and 2015 who underwent SRS (45 Gamma Knife, 11 LINAC, and 9 CyberKnife), these authors reported that SRS is a safe and effective therapy for drug-resistant TN.[29] The 11 patients treated with LINAC SRS received an 83.3 Gy mean maximal dose, with a range of maximal doses between 50 and 90 Gy. The actuarial initial freedom from pain without medications ranged between 17.3% and 76.6% (mean 49.3%, median 43.2%), and the recurrence rates were 19-63% (mean 32.2%, median 29%). In De La Pena *et al*.'s systematic review comparing CyberKnife and LINAC SRS (1705 patients in 30 articles), 63.1% of patients had an excellent response, 61.1% had a good response, and 22.5% had a recurrence.[8] Pain response, facial numbness, rates, and pain recurrence rates did not significantly differ between CyberKnife and LINAC methods.

Several studies have reported their experience with frameless SRS using a LINAC for the treatment of TN [Table 4].[4,5,8-10,14,24,26] With doses between 75 Gy and 90 Gy, the median follow-up ranged from 6 to 32 months. Most of these patients had a good or excellent response (BNI-III) to frameless LINAC SRS, with percentages of patients ranging from 69% to 100%. Minimal side effects were reported in these studies, including a temporary pain flare,[5] fatigue,[5] new hypoesthesia,[4] and ipsilateral facial numbness.[9] Two of these studies included patients who underwent either frame-based or frameless LINAC.[14,24] In Kienzler *et al*.'s study of 234 patients treated with either a 4-mm cone mask-based (97 patients) versus 5-mm cone frame-based (137 patients) LINAC technique, the patients treated with frame-based SRS had better long-term pain relief rates, fewer recurrences, and an increased interval to pain recurrence with similar toxicities compared to those who had the frameless modality.[14] In Rashid *et al*.'s study of patients who underwent frame-based (26 patients) or frameless (29 patients) LINAC SRS (all treated with 4–5 mm collimators), better pain outcomes occurred when the target definition was closer to the brainstem, and when larger target volumes were utilized.[24] A total of 63.6% of their patients had undergone treatment (MVD, percutaneous retrogasserian rhizotomy, and radiotherapy) before the LINAC SRS. There was no significant difference in terms of outcome (BNI pain and BNI hypesthesia scores) for patients with or without pretreatment, frame-based or frameless SRS, or multiple sclerosis or not multiple sclerosis-related. In De La Pena *et al*.'s study of 23 patients who underwent frameless SRS, most (69.5%) patients underwent treatment (MVD, percutaneous glycerol rhizotomy, nerve blocks, balloon compression, and radiofrequency ablation) before the LINAC SRS.[8] Seven patients were treated with two or more previous procedures.

Our study concurs with the extant literature with respect to the female predominance, older age of patients, more

Table 4: Frameless stereotactic radiosurgery using a linear accelerator for the treatment of trigeminal neuralgia.

Study	Number of patients	Dose/device/isodose Line	Follow-up (range) (months)	% Good or excellent response (BNI I-III)
Chen *et al*. 2010[4]	44	90 Gy/Novalis/brainstem exposure limited in all cases to below the 50% isodose line (range: 10–45 Gy)	15 (median)	91
Desai *et al*. 2010[9]	19	90 Gy/20–33% isodose line was allowed to touch the brainstem	13 (median)	84
Graff *et al*. 2016[10]	1	88 Gy/Varian/single point dose with the 30% isodose line abutting the brainstem	6	100
Shields *et al*. 2017[26]	20 (21 treatments)	80–85 Gy/Novalis/dose prescribed to a point in the trigeminal nerve so that at least the 60–80% isodose line encompassed the nerve	32 (median) (21.6–41.2)	95
Chou *et al*. 2018[5]	27	75 Gy/Optical surface monitoring system with cone-beam CT/Isodose line not reported	7.2 (median)	45: Pain free (18% weaned off medications, 27% continuing medications); another 45 pain improvement but not pain free; 2 (9%) no improvement
Rashid *et al*. 2018[24]	29 (frameless) 26 (frame-based)	90 Gy/Novalis/ "20% isodose line at the limit of the brainstem surface was used as constraint for the brainstem"	30.7 (mean) (2-200)	69 BNI I-IIIa, including 29% BNI I-II
De La Pena *et al*. 2022[8]	23	85 Gy/Varian/dose given in "one fraction to the isocenter as conventionally prescribed"	13.9 (median) (1.4–77.4)	35 BNI I-II and 48% BNI IIIa/b
Kienzler *et al*. 2022[14]	97 (frameless) 137 (frame-based)	90 Gy/Novalis/ "Treatment isocenters placed on the trigeminal nerve at the REZ such that the 50% isodose surface came into contact with or was slightly outside of the brainstem at the trigeminal REZ"	30.5 (median) (3–324)	88 (frameless) 93 (frame-based)
Current Study 2024	116	80–90 Gy/Novalis/ Dose prescribed to a point in the trigeminal nerve so that at least the 60–80% isodose line encompassed the nerve	38 (median) (16.7–68.0)	95

REZ: Root entry zone, BNI: Barrow neurological institute

right laterality of symptoms, and the highest percentage of patients with symptoms in the 2nd distribution of the trigeminal nerve followed by the 3rd distribution. Compared to the works of Rashid *et al*.[24] and De La Pena *et al*.[8] where the majority of their patients (64% and 69.5%, respectively) underwent either surgical or radiotherapy treatment before the frameless LINAC SRS, only 30% of patients in the present study had undergone prior interventions. More than one-third (35.3%) of patients in our study underwent a salvage procedure (MVD, rhizotomy, or an additional IGRS) following frameless IGRS, with a median duration between the initial frameless IGRS and salvage procedure of 13.6 months. This finding reflects the reported limitation of undergoing SRS compared to MVD to treat TN, specifically, the high likelihood of symptom recurrence. However, at the last follow-up, 95% of patients had a BNI score of I-III, representing excellent or good outcomes. Most importantly, the BNI score at the last follow-up was significantly lower than the BNI score before the initial frameless IGRS for patients who had a surgical/SRS intervention before the initial frameless SRS ($P < 0.001$) and for patients who did not have a surgical/SRS intervention before the initial frameless SRS ($P < 0.001$).

Our study also coincides with the literature with respect to better outcomes for patients with type 1 TN.[3,13,20,30] We demonstrated that there was a marginally significant trend toward better outcomes for Type 1 TN, indicating a 73% increase in the likelihood of treatment success for Type 1 TN. Therefore, distinguishing between Type 1 and Type 2 TN is crucial for optimized patient management and treatment planning. Our findings underscore the need for personalized therapeutic strategies based on subtype classification and highlight the potential for improved outcomes with tailored treatment approaches.

TN affects approximately 7% of patients with multiple sclerosis and is often challenging to treat with pharmacology and surgery.[6] In Conti *et al*.'s study of 27 patients with refractory TN and multiple sclerosis treated with CyberKnife SRS (maximal target dose 72.5 Gy), 23 (85%) patients achieved a BNI score of I-III within 45 days of treatment.[6] The rate of pain control decreased progressively after the 1st year, with only 44% of patients retaining pain control 4 years after SRS. Of the 11 patients with multiple sclerosis in our study, six failed IGRS, and all underwent salvage procedures. One of these patients underwent 4 salvage procedures (2 rhizotomies followed by a 2nd and 3rd frameless IGRS), while another had 1 MVD and then 2 rhizotomies. Two patients had 2 rhizotomies following the initial IGRS. All 11 patients with multiple sclerosis had a BNI score of 3 at the last follow-up. The numerous salvage procedures in these patients reflect the difficulty of treating patients with multiple sclerosis who develop TN.

Three primary percutaneous procedures are currently utilized to treat TN, including percutaneous balloon compression, glycerol rhizotomy, and radiofrequency lesioning.[31] Their method of action involves interrupting afferent pain fibers by injuring the TN root or ganglion. These three modalities may provide immediate and durable pain relief.[31] In the present study, 12 patients were treated with percutaneous interventions before the initial frameless IGRS (10 with a rhizotomy, 2 with radiofrequency lesioning). Of the ten patients who had a rhizotomy before the initial frameless IGRS, four necessitated a salvage procedure after the IGRS and all ten had a BNI score of 3 at the last follow-up. Of the two patients who underwent radiofrequency lesioning before the initial frameless IGRS, neither failed the IGRS, and both had a BNI score of 3 at the last follow-up.

Strengths and limitations of the present study

The strength of the present study is the largest group of patients, to our knowledge, with medically refractory TN who underwent frameless IGRS using the LINAC over a 10-year duration. Our study also features a long mean duration of follow-up of 44.1 months from the initial frameless IGRS (mean 55.1 months for patients who failed SRS and mean 38.0 months for those who did not). This difference likely reflects that patients who attained pain relief stopped seeking care while those with pain persistently sought help to find relief. This lengthy monitoring period permitted us to evaluate the patient's response to the frameless IGRS and offer additional surgical or SRS options if the patients did not adequately benefit from the initial treatment. Our study also shows that the time to treatment failure was marginally shorter for the patients who did not have a prior intervention. This finding is consistent with naive nerve tissue having a higher radioresistance than previously manipulated nerve. Our study adds to the flourishing literature about the importance of frameless IGRS using the LINAC for patients with medically resistant TN and highlights the need for prospective studies that assess this modality of treatment. The limitation of the present study is its retrospective nature.

CONCLUSION

Our study reported 116 patients diagnosed with medically refractory TN who underwent frameless IGRS using a LINAC over 10 years. The benefits and limitations of various modalities of SRS, as well as percutaneous procedures for TN before frameless IGRS, were presented. The challenges of treating patients with concurrent multiple sclerosis and TN, as well as the importance of distinguishing between type 1 and type 2 TN, were also discussed. In this large cohort of patients with medically refractory TN, frameless IGRS resulted in durable pain control in the majority of patients without any toxicity. While frameless IGRS delivers

precise radiation therapy in a fast and effective approach and is valuable for patients who are not appropriate surgical candidates, it is also associated with high recurrence rates.

Ethical approval

The research/study was approved by the University of Louisville Institutional Review Board, number 07.0070, dated January 09, 2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Shields LBE, Malkawi A, Daniels MW, Rao AJ, Plato BM, Yao TL, *et al*. Frameless image-guided linear accelerator (LINAC) stereotactic radiosurgery for medically refractory trigeminal neuralgia: Clinical outcomes in 116 patients. Surg Neurol Int. 2024;15:181. doi: 10.25259/SNI_101_2024