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Original Article

Outcomes using linear accelerator stereotactic radiosurgery for the treatment of trigeminal neuralgia: A single-center, retrospective study

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ABSTRACT

Background: Linear accelerator (LINAC)-based stereotactic radiosurgery (SRS) treatment of trigeminal neuralgia (TN) may have similar efficacy to Gamma Knife SRS (GK-SRS), but the preponderance of data comes from patients treated with GK-SRS. Our objective was to analyze the outcomes for LINAC-based treatment of TN in patients at our institution.

Methods: We retrospectively analyzed data for patients who underwent LINAC-based SRS for TN from 2006 to 2018. Data were collected from the patients' medical records. Nonparametric statistics were used for the analysis.

Results: Of the 41 patients treated with LINAC-based SRS (typically 90 Gy dosed using a 4 mm collimator for one fraction) during that time, follow-up data of >3 weeks post-SRS were available for 32 patients. The median pretreatment Barrow Neurological Institute (BNI) pain score was 5 (range 4–5). The follow-up period ranged from 0.9 to 113.2 months (median 5 months). There was significant improvement in postradiation BNI pain score ($P < 0.001$), with 23 (72%) patients who improved to a BNI pain score of 1–3. One patient had bothersome hypoesthesia postradiation. Approximately 38% of patients who had initial pain control had recurrence of symptoms (BNI > 3). Survival analysis showed a median time to pain recurrence of 30 months. There was no relationship between prior microvascular decompression (MVD) surgery and change in BNI pain score pre- to posttreatment.

Conclusion: The results demonstrate that LINAC-based SRS is an effective means to treat TN. Prior MVD surgery did not affect efficacy of SRS in lowering the BNI score from pre- to posttreatment in this patient cohort.

Keywords: BNI pain score, Linear accelerator, Outcomes, Pain, Stereotactic radiosurgery, Trigeminal neuralgia

INTRODUCTION

Trigeminal neuralgia (TN) is classically characterized by episodic facial pain (Type 1). Other subtypes have also been recognized that involve continuous facial pain (Type 2) or pain related to demyelinating disorders.[2,8] Although treatment with microvascular decompression (MVD) has become more common over the past decade,[15,25] noninvasive modalities of treatment such as

stereotactic radiosurgery (SRS) may be a favorable option for those patients who refuse invasive surgery or are not able to tolerate open surgical treatment.

The two most common methods of SRS are Gamma Knife (GK) and linear accelerator (LINAC). A retrospective systematic review of the techniques suggested comparable efficacies for the treatment of TN,[24] but LINAC-based treatment may be less costly for hospitals with small patient pools and does not require maintaining cobalt sources as is the case in GKS.[9,14] LINAC machines can also be used for extracranial radiation and non-SRS cranial treatments and are arguably more versatile for small community hospitals to purchase and maintain.

In this study, we retrospectively analyzed outcomes for LINAC-based treatment of TN in a group of patients at our institution. Importantly, we consistently used a radiation dose of 80–90 Gy delivered to the root entry zone (REZ) to treat our patients, which has been reported as an efficacious dose and target for the treatment of TN.[20,23,24]

MATERIALS AND METHODS

Patients

We retrospectively analyzed data for consecutive patients treated at our institution who underwent LINAC-based radiation treatment for TN from 2006 to 2018. For this Institutional Review Board (IRB)-approved case series, data were collected from the electronic medical record. Explicit patient consent was waived for this retrospective data review by the IRB. All data were deidentified for analysis. Data regarding age, sex, time of pain onset, and time of SRS procedure relative to other interventions (including MVD, percutaneous balloon rhizotomy, radiofrequency ablation, and glycerol rhizotomy) were recorded. A medical history of multiple sclerosis was also noted. Time to pain relief was determined based on clinical follow-up visit notes. Brainstem dosimetry data were also collected when available for patients.

TN type was delineated using the Burchiel classification system.[2] A Burchiel Type 1 classification refers to the classic description of TN facial pain that is episodic and unilateral for >50% of the time, separated by pain-free intervals. A Burchiel Type 2 classification refers to having continuous facial pain for >50% of the time with possible additional episodic pain. Other categories include "symptomatic trigeminal neuralgia" in patients with multiple sclerosis, atypical facial pain associated with a somatoform disorder, and trigeminal neuropathic pain associated with unintentional traumatic injury.[2] Patients with follow-up times <3 weeks were excluded from the analysis because we deemed that to be too short to reliably detect symptom changes related to radiation. Patients with SRS targets other than the REZ were also excluded from the study.

Treatment protocol

All patients underwent frame-based stereotaxis using a stereotactic Leksell head frame (Elekta Instruments AB Stockholm, Sweden). Patients then underwent a CT scan acquired with a 1–1.25 mm slice thickness for dose calculation and treatment planning purposes. Constructive interference in steady-state or 3D-fast imaging employing steady-state acquisition magnetic resonance imaging had been performed previously, and these scans were imported into the iPlan treatment planning system (Brainlab AG, Munich, Germany). These were used in combination with stereotactic T1-weighted images to identify the trigeminal nerve target and place the isocenter. After fusion with the CT scan, a treatment plan with seven arcs using a 4 mm collimator was devised. The target for all patients was the REZ of the TN in the prepontine cistern such that the brainstem contour was at the ~50% isodose line (IDL).[5,10] For most patients, the prescribed dose was 90 Gy to isocenter (100% IDL) in a single fraction. We ensured that the 20%, 30%, and 50% IDL had a mean brainstem volume of 0.14, 0.047, and 0.008 ml, respectively, per Goss *et al.*[10] Treatment was delivered on the BrainLAB Novalis LINAC device or, later, on a Varian TrueBeam (Varian, Palo Alto, CA) device. After treatment, the stereotactic frame was removed, and patients were discharged home. All patients were treated by the same team of providers.

Pain scale

The Barrow Neurological Institute (BNI) scoring system was used to quantify pain before and after the procedure.[21] A score of 1 constitutes complete pain relief without medication, a score of 2 constitutes occasional pain not requiring medication, a score of 3 constitutes some pain that is controlled on medication (subscore 3a constitutes no pain on pain medications and subscore 3b constitutes some pain that is controlled with medications), a score of 4 constitutes some pain that is inadequately controlled on medication, and a score of 5 is pain that is severe without any relief from medications. This score was determined based on patient progress notes from clinic visits.

Statistical analysis

Data analysis was done using Matlab (version 2019b, Natick, MA). The nonparametric Wilcoxon rank-sum and signed-rank tests were used for the analysis. The Kaplan–Meier estimator was used to estimate the probability of pain control (defined as a BNI <4) from time of SRS treatment in a cohort of patients who had initial pain control.[3] Censored data represented those patients who did not reach the endpoint of pain recurrence (BNI 4–5) at the time of last follow-up. Patients who were lost to follow-up were not included in the survival probability estimate.

This case series has been reported in line with the PROCESS guidelines.[1]

RESULTS

Demographics

Forty-one patients with a mean age of 67.4 (range 30–89) years were identified for inclusion. Of these, 25 (61%) had Type 1 TN, 3 (7%) had Burchiel Type 2 TN, 1 (2%) had TN related to trauma (neuropathic TN), 8 (20%) had multiple sclerosis-related TN (symptomatic TN), and 4 (10%) had atypical TN [Table 1]. Thirteen (32%) had received MVD previously and 32 (78%) had another surgical procedure such as glycerol rhizotomy before SRS. Most patients received 90 Gy of radiation prescribed to the isocenter using a 4 mm collimator for one fraction; two patients received a dose of 80 Gy. The median BNI score was 5 (range 4–5) before SRS treatment.

Outcomes after SRS

Of the 41 patients, 32 patients had sufficient follow-up data. The follow-up period varied from 0.9 to 113.2 months (median 5 months). Of these 32 patients, 23 (72%) reached a BNI pain score of 1–3. There was significant improvement in postradiation BNI score (z = 4.38, $P < 0.001$, Wilcoxon signed-rank test, [Figure 1]). Across improved patients, 13 patients had a BNI score of 3b and five patients had a BNI score of 3a after treatment. Of the 21 patients with Type 1 TN, 15 (71%) improved to a BNI score <4. Similarly, 6/7 (86%) patients with multiple sclerosis and 2/3 (67%) patients with atypical TN improved to a BNI score <4. One patient had hypoesthesia after radiation. Interestingly, there was no relationship between prior MVD surgery and change in BNI score pre- to posttreatment ($z = 1.58$, $P = 0.11$, Wilcoxon rank-sum test). Furthermore, prior history of any type of treatment did not relate to change in BNI score pre- to post-LINAC-SRS treatment ($z = -1.8$, $P = 0.07$, Wilcoxon rank-sum test).

Table 1: Demographics of 41 patients treated with LINAC for TN.

Variable	Number (%)
Mean age in years (range)	67.4 (range 30–89)
Male sex	17 (41.5)
TN type	
Burchiel Type 1	25 (61)
Burchiel Type 2	3 (7)
Related to trauma	1 (2)
Multiple sclerosis-related TN	8 (20)
Atypical TN	4 (10)
Side	
Left	16 (39)
Right	22 (51)
Bilateral	3 (7)
Distribution	
V1	1 (2)
V2	9 (22)
V3	7 (17)
V1 and V2	13 (32)
V2 and V3	8 (20)
V1, V2, and V3	3 (7)
Prior MVD	13 (32)
Prior other surgical procedure (e.g., glycerol rhizotomy)	32 (78)

TN: Trigeminal neuralgia, LINAC: Linear accelerator, MVD: Microvascular decompression

Brainstem dosimetry was retrieved for 33 patients. The median maximal dose delivered was 4500 cGy (range 1530–7020 cGy). Volumetric analysis showed that median volume of tissue that received 4500 cGy was 0.001 ml, the median volume that received 2700 cGy was 0.009 ml, and the median volume that received 1800 cGy radiation was 0.029 ml. The maximum dose to the brainstem did not relate to pain persistence (i.e., BNI score >3; Kruskal–Wallis test, Chi-squared (1) = 1.17, $P = 0.28$). Because only one patient had a documented adverse effect, dosimetric analysis on toxicity could not be performed; however, the maximum dose delivered to that patient was 4050 cGy.

A total of 12 of 32 (38%) patients had recurrence of symptoms after SRS, and 11 underwent an additional intervention such as additional SRS, rhizotomy, or peripheral electrical stimulation. Kaplan–Meier analysis of the probability of pain control from time of SRS treatment was done using a subset of patients who had initial benefit from SRS (BNI score <4). The median time to recurrence was 30.2 months (range 18.3–94 months; [Figure 2]). The "hazard rate" of pain recurrence was 8%/person-month.

DISCUSSION

TN affects 4.3 in 100,000 people/year,[13] and the treatment options vary based on the medical history and prior treatments. Radiosurgery offers a noninvasive means of treating TN, with the tradeoff that the treatment effects may take months to happen, although some effects are reported to occur as early as a few weeks,[7] and that there may be delayed complications such as hypoesthesia that can be bothersome. Several systems exist for delivering radiation to the REZ (or the Gasserian ganglion itself, although this is a less common target), namely, GKS, CyberKnife radiosurgery (CKR), and LINAC-based systems. In a recent systematic analysis, the mean rate of pain freedom in Type 1 patients with or without medication was comparable among the modalities (85% for LINAC, 87% for GKS, and 79% for CKR, meta-analysis covering studies from 1951 to 2015, [Table 2]).[4,6,11,12,17,18,22,24,26,27] These findings are comparable with our results of 72% of patients having pain control with or without medications (a BNI score of 1–3) and 71% of

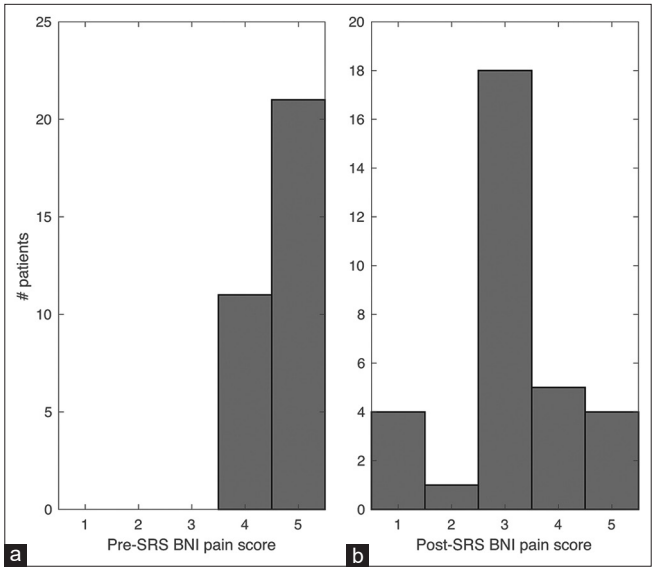

Figure 1: Histograms showing number of patients with a particular (a) pre-LINAC treatment BNI score and (b) post-LINAC treatment score. There was significant improvement in postradiation BNI score across patients (z = 4.38, $P < 0.001$, Wilcoxon signed-rank test).

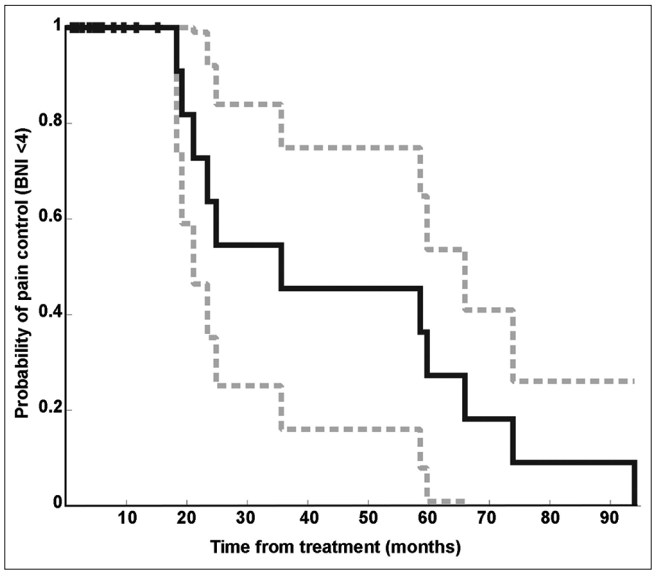

Figure 2: Kaplan–Meier survival curve showing probability of pain control (BNI < 4) decreases with time. This analysis includes only patients who had initial pain control with LINAC-based SRS treatment. Censored data are those patients who did not reach the endpoint of interest, which was documented pain recurrence at last follow-up (denoted with a "|"). The curve shows decreasing probability of continued pain control from time of intervention. A 95% confidence interval shown in dashed line.

Burchiel Type 1 patients improving. We reviewed studies published from 2016 to 2022 that reported the rate of pain treatment in patients with Type 1 TN treated with either GK or LINAC [Table 2] and found roughly 70–80% pain treatment effect (BNI 1–3) for GK and an 80–90% rate of pain control with LINAC (which is slightly better than our report). Formal meta-analysis methods are beyond the scope of this paper but suggest comparable efficacy between the modalities as shown in Tuleasca *et al.*[24]

As for other types of TN, in Pokhrel *et al.*,[19] no patients with atypical TN had improvement whereas we found 2/3 patients with atypical TN improved with SRS. We also found that 86% of patients with sensory TN (related to multiple sclerosis for our patients) achieved pain control with treatment, which is comparable with the previous findings in the literature.[16,24]

Tuleasca *et al.*[24] found the range of time to pain relief to be from 8.5 to 60 days, although estimates were biased by patient recall and were the product of follow-up appointment times not being standardized across studies. They reported that the median rate of recurrence was 29% and that time to pain recurrence was 7.5–20.4 months (meta-analysis covering studies from 1951 to 2015). Within that meta-analysis, Smith *et al.*[23] found 23% recurrence at 12.6 months. Selected LINAC studies from 2016 to 2022 [Table 2] also indicate a roughly 25–35% pain recurrence rate for Type 1 TN and perhaps 57% for all TN types.[19] We observed a probability of recurrent pain of 58% (25–84% at the 95% CI) at 30 months across TN types in our patients, and an overall recurrence rate was 38%. Nine patients were lost to follow-up after SRS treatment, which may or may not indicate that the patient had pain relief and limits the interpretation of our results. The recurrence rate was statistically lower for GK compared with LINAC treatment in Tuleasca *et al.*[24] The rate of delayed bothersome hypoesthesia in our cohort was 1/32 (3%), which is lower than one other reported study result of 13% in a larger cohort of patients, though that was not explicitly labeled as "bothersome."[23]

Interestingly, prior MVD surgery and prior surgical treatment history did not affect efficacy of SRS in lowering the BNI score from pre- to posttreatment in our cohort of patients. Tuleasca *et al.*[24] performed a pooled analysis across SRS modalities and showed that prior MVD did not affect efficacy of SRS treatment. Similarly, multivariate analysis has not shown prior surgery to relate to outcome with LINAC treatment.[20] In contrast, other studies have shown that prior treatments overall decrease the efficacy of SRS.[19,23,24] Thus, the results in this realm are mixed.

Limitations

This study has a range of limitations including being retrospective and having a relatively small sample size, although only several other studies have larger cohorts of patients treated with LINAC-based SRS for TN.[7,19,20,24] In addition, we do not have follow-up on nine patients, which

Table 2: Comparison of studies published in 2016–2022 reporting Gamma Knife or linear accelerator-based SRS treatment for Type 1 TN pain, reporting pain relief rate, recurrence rate, and time to recurrence.

Study	Cohort description	Pain relief rate	Pain recurrence rate and time to recurrence
Gamma Knife			
Tuleasca *et al.* (2018)[24]	Meta-analysis of all studies from 1951 to 2015, 5687 patients with Type 1 TN	BNI 1–3 in mean 84% (range 66.4–100%	Mean 24.6% (range 0–52%), time to recurrence 6–48 months
Martínez Moreno *et al.* (2016)[17]	117 patients with Type 1 TN	BNI 1 or 2 in 81%	32% at 24 months
Chang *et al.* (2017)[4]	130 patients with "idiopathic" TN	BNI 1–3 in 81%	Not reported
Zeng *et al.* (2018)[27]	Prospective study of 55 patients with "primary" TN	BNI 1–3 in 73%	0.9% at 2 years
Inoue *et al.* (2017)[11]	52 patients with Type 1 TN	BNI 1–3 in 67.4%	51.9% at 3.92 years (range 1.08–10.83 years)
Jung *et al.* (2017)[12]	47 patients with Type 1 TN	BNI 1–3a in 76.6%, BNI 3b in 17%	12% at 2 years 38% at 5 years
Dai *et al.* (2016)[6]	115 patients with "primary" TN	BNI 1–3 in 88.7%	10.8% at 2 years
Shrivastava *et al.* (2019)[22]	78 patients with Type 1 TN	NA	35.9% at 17 months
Mureb *et al.* (2021)[18]	404 patients with Type 1 TN	BNI 1–3a in 78.6%	42.1%, time of recurrence not reported, mean follow-up time 32 months
Wang *et al.* (2018)[26]	168 patients with Type 1 TN	BNI 1–3a in 47%, BNI 3b in 7%	BNI 1 in 61% at 5 years, median time to recurrence was 53 months
LINAC			
Tuleasca *et al.* (2018)[24]	Meta-analysis of all studies from 1951 to 2015, 511 patients with Type 1 TN	BNI 1–3 in mean 87.3% (range 75–100%)	Mean 32.2% (range 19–63%), time to recurrence 7–20.4 months
Debono *et al.* (2019)[7]	301 patients with Type 1 TN	BNI 1–3a in 90.7%	26.4% of patients had recurrence; median time to recurrence 31.6 months (range 3–120 months); actuarial rates: 23.9% at 2 years, 34.2% at 5 years
Rashid *et al.* (2018)[20]	36 patients with classic TN	BNI 1–3a in 91.6%	Not reported
Pokhrel *et al.* (2017)[19]	22 patients with Type 1 TN	BNI 1–3b in 82%	Not reported separately for Type 1 patients; of all patients, 57% had recurrence with median time to recurrence of 17 months

SRS: Stereotactic radiosurgery, BNI: Barrow Neurological Institute pain score, TN: Trigeminal neuralgia, LINAC: Linear accelerator

leaves their treatment effect unknown. Studying a larger cohort and collecting longer follow-up data with planned follow-up clinic visits would help support our results. However, we believe that our institutional experience adds to the growing body of evidence showing the efficacy and tolerability of LINAC-SRS across a variety of institutions.

CONCLUSION

LINAC-based SRS is an effective means to treat TN for those with Type 1 as well as atypical TN and TN in the setting of multiple sclerosis. Prior MVD surgery did not affect efficacy of SRS in lowering the BNI score from pre- to posttreatment in this cohort of patients. A larger cohort of patients with prior MVD treatment followed by SRS treatment would help explore this result in future studies.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

JDR has received consulting fees from Medtronic and Corlieve Therapeutics. RLJ has received consulting fees from Medtronic.

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