Stereotactic Radiosurgery for Type 1 versus Type 2 Trigeminal Neuralgias

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INTRODUCTION: **It remains unclear whether stereotactic radiosurgery (SRS) offers the same benefit for patients with type 2 trigeminal neuralgia (TN2) as for those with type 1 trigeminal neuralgia (TN1). The objective of this study is to compare the outcomes of patients with TN1 and TN2 after SRS.**

METHODS: **SRS outcomes of patients with trigeminal neuralgia treated at a single center from 1994 to 2016 were analyzed. Patients with TN1 were matched to those with TN2 in a 1:1 ratio based on sex, age, pretreatment Barrow Neurological Institute (BNI) pain score, previous treatment, previous facial numbness, and maximum dose. The primary outcome was defined as a BNI pain score of ≤3.**

RESULTS: **The matched TN1 and TN2 cohorts each comprised 56 patients. There were no differences in BNI pain scores at last follow-up, new/worse facial numbness, or pain recurrence, or time to recurrence. Time to initial pain relief after SRS was longer for patients with TN2 (5.4 vs. 4.4 months; $P = 0.0016$). Actuarial initial pain relief rates were 75%, 90%, and 90% for TN1 and 47%, 77%, and 87% for TN2 at 5, 10, and 15 months, respectively. Actuarial pain relief maintenance rates were 72%, 67%, and 52% for TN1 and 53%, 32%, and 32% for TN2 at 1, 2, and 3 years, respectively.**

CONCLUSIONS: **SRS offers similar rates of initial pain relief, pain score distribution, pain recurrence, and time to pain recurrence between patients with TN1 and TN2. The time to initial pain relief was longer for patients with TN2.**

INTRODUCTION

Trigeminal neuralgia (TN) is a recurrent, lancinating pain syndrome in the distribution of 1 or more branches of the trigeminal nerve, with an incidence of 12.6 per 100,000 person years.[1] However, TN is a heterogeneous disease, which can be further differentiated by the quality and temporal pattern of pain, as exemplified by the Burchiel classification.[2,3] Treatments for medication-refractory TN include microvascular decompression (MVD), percutaneous ablative procedures using physical, chemical, or thermal agents, and stereotactic radiosurgery (SRS). SRS has been proved to have a reasonable risk-to-benefit profile for the treatment of TN, but its effect for patients with type 2 TN (TN2) has not been rigorously evaluated.[4-8] Although most studies suggest worse outcomes for patients with TN2 compared with type 1 TN (TN1), a direct matched cohort comparison of the 2 TN subtypes has not been conducted.[9-11] Therefore, the aim of this retrospective, propensity-score matched cohort study is to compare the SRS outcomes for TN1 with TN2.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the ethical standards committee on human experimentation at our institution. Patient consent was not

Key words
- Face
- Gamma Knife
- Matched cohort
- Pain
- Radiosurgery
- Stereotactic radiosurgery
- Trigeminal neuralgia

Abbreviations and Acronyms
BNI: Barrow Neurological Institute
MVD: Microvascular decompression
SRS: Stereotactic radiosurgery
TN: Trigeminal neuralgia
TN1: Type 1 trigeminal neuralgia
TN2: Type 2 trigeminal neuralgia

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required by the committee because of the retrospective nature of the review and de-identification of data presented. This review follows the guidelines set forth by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement.

Patient Population

We performed a single-center retrospective review of a prospectively collected database for patients with TN who underwent SRS with the Gamma Knife (Elekta AB, Stockholm, Sweden) between 1994 and 2016. The inclusion criteria were as follows: 1) age ≥18 years; 2) diagnosis of TN1 (spontaneous facial pain with >50% limited to the duration of an episode) or TN2 (spontaneous facial pain with >50% constant), as defined by the Burchiel classification; and 3) Barrow Neurological Institute (BNI) pain score of 4 (some pain that is not adequately controlled with medication) or 5 (severe pain without relief) before SRS.[2,12] The exclusion criteria were as follows: 1) TN subtypes other than types 1 or 2; 2) BNI pain score ≤3; or 3) lack of posttreatment follow-up.

Radiosurgical Technique

Our institution's Gamma Knife technique has been previously described in detail.[13] A Leksell G frame (Elekta AB) was applied to the calvarium under conscious sedation with short-acting anesthetic agents. After frame placement, magnetic resonance imaging of the brain or computed tomography of the head with cisternography, if magnetic resonance imaging was contraindicated, was performed. Magnetic resonance imaging sequences obtained for planning included volumetric T1-weighted gradient-echo of the entire brain, and constructive interference in steady state through the pons, trigeminal nerves, and the skull base. In almost all instances, the cisternal segment of the symptomatic trigeminal nerve was treated using a single 4-mm isocenter to a maximum dose of 80 Gy with an isodose line of 50% (**Table 1**).

Patient Follow-Up

Patients were followed up in person at clinic visits whenever possible, or by telephone, or with local physicians if the patient could not return to the treatment center. Patients were asked to keep track of their pain response after treatment. Reductions in TN mediations were at the discretion and under the guidance of the treatment team or local physician. Patients were followed longitudinally at 6-month to 12-month intervals. Based on the patient's pain response and medications, a BNI pain score was assigned, either at the time of follow-up or retrospectively.

Data Collection

Demographic and pretreatment data included sex, age, TN type, laterality of pain, pain distribution, previous treatments, BNI pain scores, presence of facial numbness, numbness distribution, and duration of follow-up. The SRS maximum dose and number of isocenters were noted. Outcomes data after SRS included BNI pain scores at 1, 6, 12, 24, 36, and 48 months (when available), BNI pain score at last follow-up, new or worsened facial numbness, and any additional interventions for persistent or recurrent TN. The primary outcome (pain relief) was defined as a BNI pain score of ≤3 after SRS. Initial pain relief was defined as the first instance that the patient achieves a BNI pain score of ≤3 after SRS.

Statistical Analysis

Propensity-score matching was performed using R (version 3.3.2 [R Foundation for Statistical Computing, Vienna, Austria]) with dplyr and MatchIt packages. TN1 and TN2 patients were matched in a 1:1 ratio without replacement and with a caliper width of 0.2, based on gender, age, pre-SRS BNI pain score, any previous treatment, any previous facial numbness, and maximum dose as covariates. Subsequent statistical analyses were performed to compare the baseline and outcomes data of the matched TN1 and TN2 cohorts using Stata (version 14.2 [StataCorp, College Station, Texas, USA]). Continuous variables were compared using a Student t test or Mann-Whitney U test, as appropriate. Categorical variables were compared using a Pearson χ^2 test or Fisher exact test, as appropriate. Statistical significance was defined as $P < 0.05$, and all tests were 2 tailed. Time-dependent analyses for pain relief and pain recurrence were performed using Kaplan-Meier and actuarial methods, and differences between function curves were analyzed using the Wilcoxon test. Missing data were not imputed.

RESULTS

Description of the Study Cohorts

Between 1994 and 2016, 630 patients with TN underwent SRS at our institution. Data were available on 260 patients, comprising 194 patients with TN1 and 64 patients with TN2. Two patients did not fit the diagnosis of TN1 or TN2. After the application of inclusion and exclusion criteria, the matching process yielded 56 patients in each of the TN1 and TN2 cohorts. **Table 1** compares the baseline characteristics of the matched TN1 and TN2 cohorts. The proportion of female gender was 63% and 59% for the TN1 and TN2 cohorts, respectively, and the mean ages were 63 and 62 years, respectively. There were no differences between the 2 cohorts regarding baseline BNI pain scores, duration of symptoms before SRS treatment, pain distribution, pain laterality, previous treatments, previous facial numbness, isocenters used, and maximum dose delivered. The mean follow-up duration was longer in the TN1 cohort (29 vs. 18 months; $P = 0.02$).

Pain Relief After SRS

Table 2 compares the outcomes of the matched TN1 and TN2 cohorts after SRS. Initial pain relief was achieved in 89% and 80% of TN1 and TN2, respectively ($P = 0.19$). There was no difference in BNI pain score distribution at last follow-up ($P = 0.29$). The mean time to initial pain relief was significant longer for the TN2 cohort (5.4 vs. 4.4 months, $P = 0.0016$; **Figure 1A**). The actuarial rates of initial pain relief were 75%, 90%, and 90% at 5, 10, and 15 months, respectively, for TN1, compared with 47%, 77% and 87% at 5, 10, and 15 months, respectively, for TN2.

We performed subgroup analyses based on BNI pain score before SRS. Patients with TN1 with a baseline BNI pain score of 4 showed a shorter time to initial pain relief compared with those with TN2 (**Figure 1B**; $P = 0.0230$). For patients with a BNI pain score of 4, the actuarial rates of initial pain relief rates were 74%, 90%, and 90% at 5, 10, and 15 months, respectively, for TN1, compared with 51%, 85%, and 92% at 5, 10, and 15 months, respectively, for TN2. Patients with TN1 with baseline