

Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: implications of treatment and critical review of the literature

Clinical article

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Object. Few long-term studies of Gamma Knife surgery (GKS) for trigeminal neuralgia (TN) exist. The authors report their long-term experience with the use of GKS in a previously reported cohort of patients with TN that has now been followed since 1996.

Methods. One hundred twelve patients with TN were treated with GKS at the University of Maryland between June 1996 and July 2001. Of these, 67% had no invasive operations for TN prior to GKS, 13% had 1, 4% had 2, and 16% had ≥ 3. The right side was affected in 56% of cases, predominantly involving V2 (26%), V3 (24%), or a combination of both (18%) branches. The median age at diagnosis was 56 years, and median age at GKS was 64 years. The median prescription dose of 75 Gy (range 70–80 Gy) was delivered to the involved trigeminal nerve root entry zone. The authors assessed the degree of pain before and after GKS by using the Barrow Neurological Institute (BNI) pain scale.

Results. In total, 102 patients took the survey at least once, for a response rate of 91%. Although not found to alter the conclusions of this study, 7 cases of atypical TN were found and these patients were removed, for a total of 95 cases herein analyzed. The median follow-up was 5.6 years (range 13–115 months). Before GKS, 88% of patients categorized their pain as BNI IV or V (inadequate control or severe pain on medication), whereas the remainder described their pain as BNI III (some pain, but controlled on medication). After GKS, 64% reported a BNI score of I (no pain, no medications), 5% had BNI II (no pain, still on medication), 12% had BNI III, and 19% reported a BNI score of IV or V. The median time to response was 2 weeks (range 0–12 weeks) and the median response duration was 32 months (range 0–112 months). Eighty-one percent reported initial pain relief, and actuarial rates of freedom from treatment failure at 1, 3, 5, and 7 years were 60, 41, 34, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment versus those in whom a previous surgical intervention had failed (32 vs 21 months, $p < 0.02$). New bothersome facial numbness was reported in 6% of cases.

Conclusions. This study represents one of the longest reported median follow-up periods and actuarial results for a cohort of patients with classic TN treated with GKS. Although GKS achieves excellent rates of initial pain relief, these results suggest a steady rate of late failure, particularly among patients who had undergone prior invasive surgical treatment. Despite a higher than expected recurrence rate, GKS remains a viable treatment option, particularly for patients who have had no prior invasive procedures. Patients with recurrences can still be offered salvage therapy with either repeat GKS, microvascular decompression, or rhizotomy. (DOI: 10.3171/2009.2.JNS08977)

KEY WORDS • trigeminal neuralgia • Gamma Knife • radiosurgery

WITH > 15,000 new cases each year, TN is a debilitating illness characterized by severe, unilateral, electrical shock–like pain occurring in the distribution of the trigeminal nerve.¹² Since its first description by Aretaeus of Cappodocia in the 2nd century,^{26,27} the diagnosis of TN has evolved tremendously. The International Headache Society has defined TN pain as the following: 1) paroxysmal attacks, lasting from 1 second to 2 minutes, affecting ≥ 1 division of the trigemi-

nal nerve; 2) pain that is intense, sharp, superficial, or stabbing, precipitated from trigger areas or factors; 3) attacks stereotyped in the individual patient; 4) no clinically evident neurological deficit; and 5) pain not attributed to another disorder.¹¹

Numerous treatment options exist for patients who suffer from TN. In most patients the pain is initially managed pharmacologically with anticonvulsant or antidepressant medications. However, both classes of medications are associated with a wide variety of side effects, including sedation, impaired memory, peripheral neuropathy, confusion, tremors, nausea, and insomnia, to name a few.^{28,30} More invasive procedures such as percutaneous rhizotomies and MVDs are reserved for patients in whom

Abbreviations used in this paper: BNI = Barrow Neurological Institute; GKS = Gamma Knife surgery; MVD = microvascular decompression; TN = trigeminal neuralgia.

either medical management has failed or who cannot tolerate the adverse side effects associated with use of the medications. Despite achieving high initial response rates, percutaneous rhizotomies often fail to maintain a durable response of pain relief.^{32,35} On the other hand, MVD has a well-documented history of establishing durable pain control.^{1,5,16,17,33} However, this is an invasive procedure involving an open craniotomy, and it requires hospitalization of the patient. Radiosurgical management of TN was pioneered by Lars Leksell in 1951.¹⁵ Since then numerous groups have demonstrated the effectiveness of radiosurgical procedures in the treatment of TN, with initial response rates ranging from 50 to 96%.^{6,9,10,13,14,18,23,25,29,31}

At the University of Maryland Medical Center, 367 cases of TN have been treated with GKS between 1996 and 2007. We previously reported our outcomes at a median follow-up duration of 30 months.²¹ Sparse data exist in the literature in terms of long-term follow-up for patients with classic TN who have been treated with radiosurgery, and even less actuarial data exist to predict long-term outcomes for patients who have initially responded to radiosurgical therapy. Many series in the literature simply report initial rates of pain relief following radiosurgery, and only give the crude percentage of patients who remain pain free at last follow-up. For a true understanding of the efficacy of a treatment, actuarial analysis must be performed with substantial follow-up. The purpose of this study was to update the long-term outcomes in the series of patients treated between June 1996 and July 2001, now with a median follow-up of 67 months (5.6 years).

Methods

Patient Characteristics

Between June 1996 and July 2001, 112 patients were treated with GKS for TN at the University of Maryland Gamma Knife Center. Patient characteristics are described in Table 1. Briefly, the median age at diagnosis was 56 years (range 17–88 years), and the median age at time of GKS was 64 years (range 24–96 years). The median duration of symptoms was 57 months (range 2–480 months). A majority of the patients were female, and the right side of the face was more commonly afflicted. One patient had bilateral involvement and received GKS to both trigeminal nerves. The V2 and V3 nerve branches, or a combination of both, were more frequently involved, whereas in 13% of cases all 3 branches were involved. The majority of patients underwent GKS after pharmacological management failed, but 33% underwent GKS after undergoing at least 1 or more prior invasive procedures, most commonly percutaneous rhizotomy or MVD. The decision to proceed with GKS instead of an invasive procedure was almost universally driven by patient choice.

Radiosurgical Technique

All patients were treated on the 201-source ⁶⁰Co Gamma Knife unit manufactured by Elekta Instruments. Treatment planning was performed jointly by a radiation oncologist, neurosurgeon, and medical physicist for all cases. After induction of local anesthesia, the Leksell

TABLE 1: Pretreatment characteristics of 112 patients with classic TN

Characteristic	Value
median age at diagnosis in yrs (range)	56 (17–88)
median age at time of GKS in yrs (range)	64 (24–96)
median duration of symptoms in mos (range)	57 (2–480)
sex	
male	35%
female	65%
side affected	
rt	56%
lt	42%
bilat	1%
nerve branch affected	
V1	5 (4%)
V2	29 (26%)
V3	27 (24%)
V1 + V2	13 (12%)
V1 + V3	0 (0%)
V2 + V3	20 (18%)
V1 + V2 + V3	15 (13%)
not documented	3 (3%)

Model G stereotactic coordinate frame was affixed to the head of each patient, and contrast enhanced MR imaging was performed to visualize and target the trigeminal nerve root entry zone. A single 4-mm isocenter was placed adjacent to the trigeminal nerve root entry zone. The median prescription dose (maximal dose) for the treatment was 75 Gy (range 70–80 Gy) delivered to the involved trigeminal nerve root entry zone. A plugging pattern typically blocking 32 sources was used so that the surface of the brainstem was irradiated at no greater than the 20% isodose line for any patient (Fig. 1).

Follow-Up and Statistical Analysis

Treatment outcomes were assessed by patient self-reports of pain control and medication usage at all follow-up visits. Pain outcomes were assessed using the BNI pain scale²⁵ before GKS, after GKS, and at each subsequent follow-up visit (Table 2). Initial response was defined as an improvement in patient-reported BNI score to a level of BNI I, II, or III. Pain outcomes were further classified as excellent (BNI I or II; no medication required), good (BNI III; some pain, adequately controlled with medication), fair (BNI IV; some pain, not adequately controlled with medication), and poor (BNI V; severe pain/no pain relief). Treatment failure was defined as pain returning to a BNI level of IV or V, or the patient undergoing an invasive surgical procedure due to uncontrolled pain. Patients with BNI IV or V after GKS were considered to have severe pain unresponsive to GKS, and these cases were thus categorized as treatment failures. All patients were evaluated regularly by their physicians, and the pain medications were tapered judiciously by the treating physician only when adequate pain relief was achieved.

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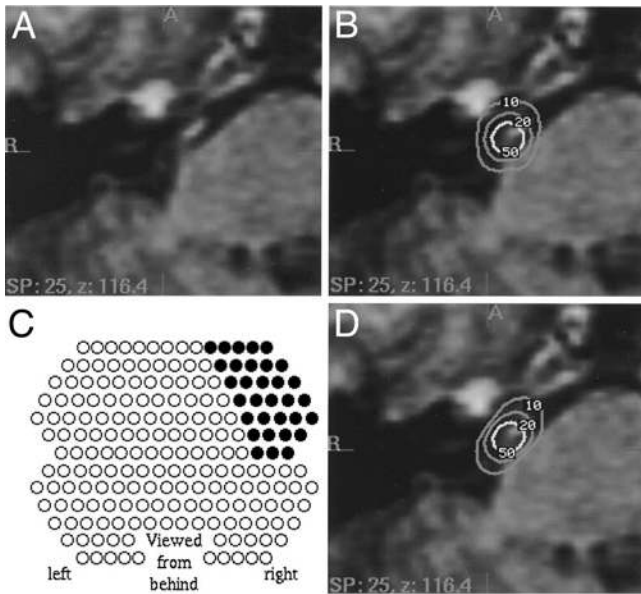


FIG. 1. Contrast-enhanced MR imaging demonstrating an affected trigeminal nerve (A), with isodose lines shown before (B) and then after (D) using the 32-plug blocking pattern depicted in the accompanying schematic (C).

Given that the University of Maryland is a major referral center for GKS and patients often come from far away for their treatment, assessment of pain outcomes according to the BNI pain scale was often established through serial telephone interviews by a trained volunteer.

Actuarial analyses on freedom from treatment failure were calculated by the product-limit method of Kaplan and Meier. The Wilcoxon rank-sum test was used to make group comparisons of median time to pain relief and median duration of pain relief. The Wilcoxon signed-rank test was used to compare distributions of BNI classes before and after GKS. All statistical calculations were performed using SPSS software, version 13.0.

Results

Initial Pain Outcomes

Of the 112 patients treated between June 1996 and July 2001, only 10 have been lost to follow-up. Although they were found not to alter the results of this study, 7

cases of atypical TN were excluded from analysis. Atypical TN was defined as the following: 1) pain occurring in the trigeminal nerve distribution; 2) continuous pain without pain-free periods; 3) pain with no definite triggers; 4) pain that was burning or aching in nature, rather than the typical lancinating or electrical pain more commonly described with classic TN; and 5) pain that was not attributable to any other disorder. Using these strict criteria, we have previously reported on our outcomes of GKS for atypical TN.⁸ The median follow-up for the remaining 95 patients was 5.6 years (range 1–10 years). Prior to undergoing GKS, 88% of patients categorized their pain as BNI IV or V, whereas the remainder described their pain as BNI III. No patient classified their pretreatment pain as BNI I or II. After GKS, 64% scored their pain as BNI I, 5% as BNI II, 12% as BNI III, and 19% as BNI IV or V ($p < 0.001$). Therefore, the initial response rate to GKS, as defined by an improvement in BNI score (either BNI I, II, or III), was 81%. The median time to pain relief was 2 weeks (range 0–12 weeks), with 40% experiencing pain relief within 1 week. Of the entire cohort, 70% were able to decrease or discontinue the use of medications in the management of their TN symptoms. Despite improvement in pain, many patients were reluctant to discontinue the use of their medications due to fear of pain recurrence. Of the 19% of patients not initially responding to GKS, none were able to decrease their dose or frequency of usage of the medications necessary to control their TN symptoms.

Initial response rates for the patients with no prior surgeries were similar to the initial response rates for patients who had undergone previous invasive surgical procedures (81 vs 77%, $p = 0.42$). The same was true with the median time to relief between the 2 groups (2 vs 3 weeks, $p = 0.10$). There was no difference in the initial response rates or median time to relief based on the dose of radiation delivered.

Long-Term Pain Outcomes

Treatment failure was defined as pain returning at a BNI level of IV or V, or any patient undergoing an invasive surgical procedure due to pain recurrence. Thus far, of the 77 patients experiencing initial pain relief, 43 (56%) suffered treatment failure. The median duration of relief for the entire cohort was 32 months (range 0–112 months). Actuarial analysis using the method of Kaplan and Meier

TABLE 2: Pain intensity scales from the BNI and the Mayo Clinic

BNI		Mayo Clinic	
Grade	Description	Grade	Description
I	no trigeminal pain, no medication	excellent	no pain & no medication
II	occasional pain, not requiring medication	good	no pain & reduced level of medication
III	some pain, adequately controlled by medication	fair	significantly less pain & fewer medications required
IV	some pain, not adequately controlled by medication	poor	no significant change in pain or medication requirement
V	severe pain/no pain relief		

was used to assess the freedom from treatment failure. Duration of freedom from treatment failure was defined from the day of GKS. Therefore, any patient who never responded to GKS was scored as having 0 months of pain relief. The 1-, 2-, 3-, 4-, 5-, 6-, and 7-year freedom from treatment failure was 60, 51, 41, 34, 34, 30, and 22%, respectively (Fig. 2 upper). Although initial response rates and median time to relief were similar in the 2 groups of patients as described above, the median duration of relief was statistically longer for patients who had not undergone a prior invasive surgical procedure (32 months) compared with the group of patients who received GKS after an invasive surgical procedure failed (21 months, $p = 0.02$). The 1-, 2-, 3-, 4-, 5-, 6-, and 7-year freedom from treatment failure was 81, 53, 50, 41, 30, 23, and 23% for patients who had not undergone invasive surgical procedures prior to GKS, compared with 61, 35, 20, 15, 15, 7, and 7% for patients who had undergone invasive surgical procedures prior to GKS (Fig. 2 lower, $p = 0.02$). There was no difference in duration of pain relief based on dose of radiation delivered.

Salvage GKS

Of the 62 patients who experienced a failure of initial GKS (including the patients who never responded to GKS), 30 underwent a repeat GKS procedure. The median prescription dose (maximum dose) delivered for the second GKS was 70 Gy (range 45–75 Gy). The initial response rate after the repeat GKS was 68%. Long-term outcomes in this group of patients will be reported after longer follow-up in a separate report.

Posttreatment Complications

There were no major complications noted among the patients undergoing GKS. Only 6% of patients experienced new bothersome facial numbness after initial GKS. Two cases of new facial numbness arose > 2 years after GKS in the absence of any other procedures before or after GKS that could be considered confounding factors. However, of these 2 patients, only 1 characterized the numbness as bothersome.

Discussion

Patients suffering from TN have a variety of treatment options available to them, such as medical management, percutaneous rhizotomies, MVD, and GKS. When assessing the effectiveness of any of these therapies, it is essential to evaluate the initial response rate of a treatment as well as the durability of the response. Numerous retrospective reports clearly document the initial effectiveness of GKS. However, long-term follow-up of patients is often lacking, and thus makes the durability of response difficult to assess. To our knowledge, our experience provides actuarial analysis of treatment success with the longest reported median follow-up in a cohort of patients suffering from TN.

Initial Response Rate

A significant challenge in analyzing the TN litera-

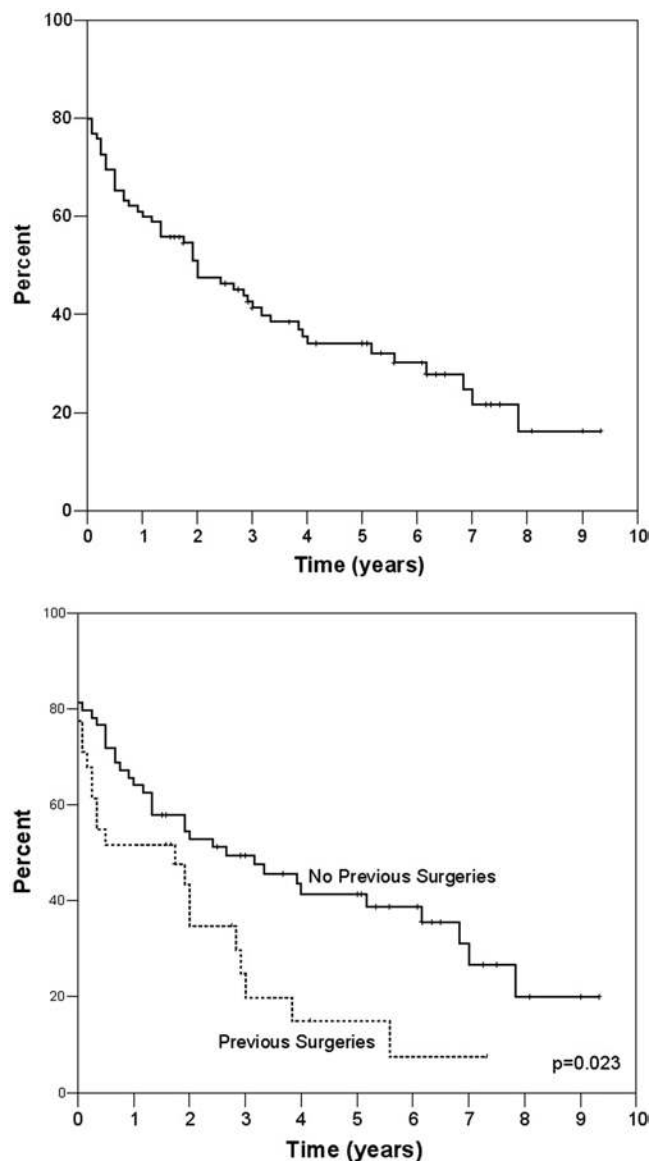


FIG. 2. Upper: Actuarial plot demonstrating 1-, 3-, 5-, and 7-year rates of freedom from severe pain (BNI IV or V) of 60, 41, 34, and 22%, respectively, after GKS for classic TN. Lower: Actuarial plot demonstrating rates of freedom from severe pain (BNI IV or V) for patients treated with GKS for classic TN, stratified by history of prior invasive surgical procedures.

ture centers on the lack of a standardized definition of treatment response. Nearly every institution that reports on pain outcomes for patients treated with GKS uses a different definition. For instance, in the multiinstitutional experience reported by Kondziolka et al.¹³ in 1996, pain relief was coded by the patient and surgeon by using a scale of improvement from 0 to 100%. Response was further characterized as poor (0 to < 50% improvement), good (50–90% improvement), and excellent (100% improvement). Like most assessments of pain, this scale is subjective. More importantly, it does not take into account issues that may influence pain scores, such as medication usage or invasive procedures. Brisman³ used a scale that attempted to take into account a scale of improvement

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ranging from 0 to 100% as well as medication usage. Response was broken down into 5 groups: 1) complete pain relief, no medications needed; 2) $\geq 90\%$ pain relief, including "small doses of medicines"; 3) 75–89% pain relief; 4) 50–74% pain relief; and 5) $< 50\%$ pain relief. This scale is again limited by the subjectivity of what is considered a small dose of medicine to control symptoms. The Mayo Clinic^{22,23} and the BNI²⁵ have used similar scales with minor differences to assess pain outcomes that more adequately address the issue of medication usage (Table 2).

In our report we used the BNI scale, and further classified BNI scores as excellent (BNI I and II), good (BNI III), and poor (BNI IV and V). Our initial response rate, defined as an improvement in BNI scale score to either I, II, or III, was 81%. This initial response rate is similar to other experiences reported in the literature.^{9,13,14,18,20,24,34}

The difficulty in assessing rates of pain relief is not limited to the radiosurgical literature. Although MVD has a much longer history than GKS in the treatment of TN, each institution uses a different definition of pain relief and pain recurrence.^{1,5,32,33} Perhaps the most stringent definition of pain response was used by Tronnier et al.³² in their report comparing MVD and radiofrequency rhizotomy. In this report, "pain free" was defined as having no pain and not using any medications to control pain. The authors note that patients who were able to control their pain with medications and were satisfied with the procedure were still considered to have experienced treatment failure. Unfortunately, the authors do not indicate in their results the initial rate of pain relief, but rather only report on the outcomes of the patients who responded to the invasive surgical procedure.

Durability of Pain Relief

The second major difficulty in analyzing the TN literature is determining the durability of pain relief. Some studies simply ask patients whether they are pain free at time of follow-up and do not take into account confounding factors such as medication usage and dosage or the performance of invasive procedures.²⁹ Other reports assess pain outcomes during follow-up visits or through questionnaires with a percentage-improvement score at time of last follow-up.^{2,3} A limitation of this methodology is that it does not take into account a worsening percentage-improvement score. For instance, at one visit a patient may claim to have 80% pain improvement, but 1 year later he or she may report only 50% pain improvement. The physician may score this as continued pain relief, but the patient may consider this recurrence. Rogers et al.²⁵ defined recurrence as any worsening of pain from the maximal level of relief, and included any patient who resumed pharmacological therapy after having stopped TN medications, even if pain control was reattained. This would be an ideal definition, especially for patients who are followed prospectively and who can detail their medication history. However, using this definition of pain recurrence in a retrospective fashion is difficult even for the most accurate patient historian. It also does not take into account the patient who perhaps never discontinued pain medications despite having complete pain relief, because of a fear of recurrent pain.

Because it is very difficult for a patient suffering from TN to document their pain medication regimens accurately, especially when multiple physicians are involved in their care, we chose to use a definition of pain recurrence that included pain worsening to a BNI score of IV (some pain, not adequately controlled with medication) and V (severe pain/no pain relief), or pain returning to a level that influenced the patient to undergo an invasive surgical procedure. Our actuarial data demonstrate that the 1-, 2-, 3-, 4-, 5-, 6-, and 7-year rates for freedom from treatment failure were 60, 51, 41, 34, 34, 30, and 22%, respectively. Had we included in our definition of pain recurrence any patient who reinitiated pain medications after being pain free while off TN medications, or patients who simply required an increase in their dose of pain medications to manage symptoms after a successful GKS, then clearly our actuarial rates of freedom from treatment failure would be even worse.

Some reports on the effectiveness of GKS in the treatment of TN simply give the percentage of patients who are pain free at last follow-up visit.^{3,9,13,14,20,22} This methodology also has limitations, because by definition 50% of patients have not had the median follow-up period. Reporting the percentage of patients who are pain free at last follow-up does not help physicians counsel their patients as to the likelihood that they will be pain free at a certain time point. This particular analysis can only be achieved by Kaplan-Meier actuarial analyses. A Kaplan-Meier analysis is useful to estimate survival (in this case, survival free from treatment failure) for a group of patients who have varying lengths of follow-up. In almost all other disease sites treated by physicians in which there is an expected risk of disease recurrence, Kaplan-Meier actuarial analyses are used to estimate the probability of being alive, dead, or free of a disease. We cannot appropriately counsel a patient with a malignant disease as to their chances of achieving a cure of that particular malignancy if the literature only reports on the percentage of patients alive at last follow-up. By the same rationale, we cannot adequately advise our patients with TN based on literature that only provides the percentage of patients free from pain recurrence at last follow-up.

We are not the first group to publish actuarial analyses of freedom from pain recurrence.^{2,18,23,25,31} However, in these previous reports, the longest reported median follow-up period was 26 months.²³ In that Mayo Clinic report, excellent or good outcomes were achieved and maintained in 65 and 55% of patients at 1 and 3 years, respectively, after GKS. Excellent outcomes were defined as complete pain relief without medication, whereas good outcomes were defined as no pain and reduced level of medications. In the report published by Tawk and associates,³¹ excellent response was defined by complete resolution of pain without medication. Good response included patients whose pain was well controlled but who continued to receive medical management as well as patients who had residual pain but managed to remain off medications. Fair response included patients who experienced modest pain relief and continued pharmacological management. In their actuarial analysis, there is a steady rate of pain recurrence at a median follow-up of 24 months, with ~ 65 and 45% of patients achieving

a durable response at 1 and 2 years after GKS. Finally, in the University of Pittsburgh experience,¹⁸ excellent response was characterized by complete pain relief without medications; good response included patients with complete pain relief but still using some medications; and fair response included patients with > 50% pain relief. At a median follow-up of 24 months, excellent, good, and fair outcomes were achieved and maintained in 76, 71, 67, and 56% of patients at 1, 2, 3, and 5 years after GKS. However, when only patients with excellent or good outcomes were examined, the 1-, 2-, 3-, and 5-year rates of pain relief dropped to 64, 59, 57, and 38%, respectively. With longer follow-up, one may assume that more patients may experience recurrence, and thus these actuarial rates of pain relief may continue to decrease. Our report is on a cohort of patients with a median follow-up of 5.6 years, much longer than the aforementioned experiences. Therefore, the 1-, 2-, 3-, and 4-year rates of freedom from pain recurrence that we have reported are probably quite accurate given the length of median follow-up for the cohort.

As stated earlier, MVD has a longer history in the literature, with Dandy⁷ addressing the possible cause of TN in 1934. Barker et al.¹ reported on the long-term outcomes of 1185 patients with TN treated with MVD over a 20-year period. More than 1000 patients in this cohort had been followed for at least 1 year, and the median follow-up period was 6.2 years. Similar to our study, only 10% of patients were lost to follow-up. Excellent outcomes were defined as the absence of lancinating facial pain, or a reduction in pain of at least 98%, without the use of medications. Good outcomes were defined as 75% reduction in pain as assessed by the patient, and intermittent treatment with low doses of medication was allowed in this category. The actuarial rates of achieving and maintaining excellent or good outcomes following MVD at 1 and 10 years was 84 and 68%, respectively, with a plateau appearing in the graph at ~ 7 years post-MVD. Tronniier et al.³² reported similar results after a mean follow-up of 10.9 months, although the cohort consisted of 225 patients undergoing MVD for TN. Lastly, Broggi et al.⁴ reported on 148 patients with TN treated with MVD, and this study had a mean follow-up of 38 months. The probability of being pain free 3 years after MVD was ~ 75%. Taken together, these reports would indicate that MVD provides durable pain relief for patients with TN.

Direct comparisons of GKS and MVD are difficult due to the bias of patient selection when offering these 2 procedures to a patient. The median age of patients at the time of GKS in our report was 64 years, whereas the median age of patients undergoing MVD in the aforementioned studies was nearly a full decade younger. Compared with MVD, GKS is a relatively noninvasive procedure that does not require an inpatient hospitalization. On the other hand, MVD is an invasive procedure requiring an open craniotomy. Side effects of MVD include CSF leakage (1–5%), meningismus (15–17%), and hearing loss (1–7%).^{1,4,33} Like any invasive surgical procedure, MVD carries a risk of death secondary to bleeding, infection, or complications from general anesthesia. However, it should be noted that in the previously cited studies the mortality rate was universally < 1%.

Treatment with GKS appears to be more effective

in patients who have had no prior invasive surgical procedure. In our study, a majority of patients had not undergone such a procedure. Although the rates of initial pain relief and median time to pain relief were similar between the 2 groups, patients who had undergone a prior invasive surgical procedure were less likely to achieve durable pain control when compared with the group of patients who had not undergone such a procedure. A history of a prior invasive surgical procedure predicting for worse outcome after GKS has been shown by others as well.^{18,23,24,31} Therefore, GKS should still be offered to patients with TN as a first-line therapy after pharmacological management has failed. Doing so may help patients delay or even avoid an unnecessary invasive surgical procedure.

Future Directions

The limitations of this study relate to biases associated with any retrospective analysis. When follow-up spans many years, it is often difficult for patients to remember details of their disease management, or to quantify pain outcomes by using a percentage scale. It is even more difficult for patients to remember their medication history over the course of a follow-up period. However, in our experience, patients often vividly remember the day their pain returned to a level so severe that medications no longer controlled their symptoms. Regis et al.²⁴ have successfully completed a prospective analysis of GKS for the treatment of TN, and included validated quality of life measurements and detailed somatic sensory perception testing. The 100 patients reported in their study had a minimum follow-up of 1 year, but the median length of follow-up is not reported. The authors classify pain outcomes as follows: pain free without medication (Class I); pain free with medication (Class II); pain frequency reduction > 90% (Class III); pain frequency reduction between 50 and 90% (Class IV); no significant reduction in pain frequency (Class V); and pain worsening (Class VI). In this report, the rate of initial pain relief was 94%, but it is unclear which classes of response were included in their definition of pain relief. Given that the data are being collected prospectively in their study, it will be interesting to see if actuarial analysis of freedom from pain recurrence is maintained with longer follow-up. Regardless, Regis and associates should be commended for attempting the prospective evaluation of the outcomes of patients with TN treated with GKS.

Despite our study being retrospective in design, we believe the data to be meaningful in describing a steady rate of failure after GKS. Prospective studies will help us obtain a more accurate picture of recurrence patterns following a successful GKS. A possible explanation for the recurrences relates to the dose of radiation used in this cohort of patients (median dose 75 Gy). Although there was no obvious dose-response relationship identified in our study, the range of doses delivered was 70–80 Gy. Of the 95 patients reported in this study, only 7% received less than the median dose, and only 17% received greater than the median dose, thus limiting our ability to make meaningful conclusions about the dose-response relationship. One of the early reports of the use of a higher dose

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of radiation came from University of Kentucky, where a cohort of 42 patients was treated with a maximum dose of 90 Gy.²⁰ The authors state that the change to treating patients upfront with 90 Gy occurred after several patients early on in their experience with 70 Gy suffered from an early relapse of pain. With a median follow-up of 14 months, 74% of patients experienced some form of pain relief. This increased dose of radiation was associated with a facial numbness rate of ~ 17%, nearly double that which is reported in the literature in studies in which lower doses of radiation were used. The durability of the pain relief is not calculated with actuarial analyses, so it is difficult to comment on the likelihood of pain recurrence with the 90-Gy dose. Researchers at the Mayo Clinic have compared outcomes of patients treated with 70 Gy versus 90 Gy.²² Rates of initial pain relief were similar, although the group treated to a lower dose underwent more additional surgeries after GKS compared with the group that received 90 Gy, thus suggesting greater efficacy with higher-dose radiation. Again, patients treated to the higher dose experienced higher rates of trigeminal nerve dysfunction, with nearly one-third of them complaining of bothersome dysesthesias that negatively impacted their activities of daily living. Overall, these and similar results on dose escalation,¹⁹ coupled with our own institution's long-term results of GKS for TN, lend support for the development and implementation of a randomized controlled trial comparing low-dose with high-dose GKS.

Conclusions

This study represents one of the longest reported median follow-up periods and actuarial results for a cohort of patients with classic TN treated with GKS. Although GKS achieves excellent rates of initial pain relief, our results suggest a steady rate of late failure, particularly among patients who have had prior invasive surgical treatment. Despite the higher than expected recurrence rate, GKS remains a viable treatment option, particularly for patients who have had no prior invasive procedures. These results will help practitioners counsel patients better regarding the likelihood of achieving durable pain control. Patients with recurrences can still be offered salvage therapy with either a repeat GKS procedure or MVD.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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