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REPEAT GAMMA KNIFE RADIOSURGERY FOR TRIGEMINAL NEURALGIA

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Abstract

Purpose—Repeat gamma knife stereotactic radiosurgery (GKRS) for recurrent or persistent trigeminal neuralgia induces an additional response but at the expense of an increased incidence of facial numbness. The present series summarized the results of a repeat treatment series at Wake Forest University Baptist Medical Center, including a multivariate analysis of the data to identify the prognostic factors for treatment success and toxicity.

Methods and Materials—Between January 1999 and December 2007, 37 patients underwent a second GKRS application because of treatment failure after a first GKRS treatment. The mean initial dose in the series was 87.3 Gy (range, 80–90). The mean retreatment dose was 84.4 Gy (range, 60–90). The dosimetric variables recorded included the dorsal root entry zone dose, pons surface dose, and dose to the distal nerve.

Results—Of the 37 patients, 81% achieved a >50% pain relief response to repeat GKRS, and 57% experienced some form of trigeminal dysfunction after repeat GKRS. Two patients (5%) experienced clinically significant toxicity: one with bothersome numbness and one with corneal dryness requiring tarsorrhaphy. A dorsal root entry zone dose at repeat treatment of >26.6 Gy predicted for treatment success (61% vs. 32%, $p = .0716$). A cumulative dorsal root entry zone dose of >84.3 Gy (72% vs. 44%, $p = .091$) and a cumulative pons surface dose of >108.5 Gy (78% vs. 44%, $p = .018$) predicted for post-GKRS numbness. The presence of any post-GKRS numbness predicted for a >50% decrease in pain intensity (100% vs. 60%, $p = .0015$).

Conclusion—Repeat GKRS is a viable treatment option for recurrent trigeminal neuralgia, although the patient assumes a greater risk of nerve dysfunction to achieve maximal pain relief.

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Keywords

Gamma knife; Radiosurgery; Trigeminal neuralgia; Toxicity; Repeat

INTRODUCTION

Gamma knife radiosurgery (GKRS) is an effective treatment of trigeminal neuralgia (TN). Previous series have shown the benefit to be a 50% reduction of pain in 77–95% of patients treated with GKRS (1–16). Repeat GKRS for recurrent TN has also been proved efficacious, although to date, only a limited number of small series with a combined total of 308 patients have been reported worldwide (17–25). Because of the small sample sizes, controversy has arisen regarding the optimal dose and location for repeat treatment (19–21, 23, 25, 26). Moreover, the risk factors for repeat treatment success and failure have not been consistently identified.

The goal of the present retrospective study was to report the outcomes of patients who had undergone a second GKRS for recurrent TN at Wake Forest University Baptist Medical Center. The dosimetric data were analyzed with regard to the dose, isocenter location, and isocenter distance from several important anatomic landmarks to elucidate any relationship among the dose, isocenter location, and treatment outcomes. Medical comorbidities, including multiple sclerosis, hypertension, and diabetes, were also evaluated for their correlation with treatment success or failure.

METHODS AND MATERIALS

Patients

Between January 1999 and December 2007, 652 patients underwent GKRS for medically refractory TN using the Leksell Gamma Knife (Elekta, Norcross, GA) at Wake Forest University Baptist Medical Center. The outcomes from the initial 256 patients, including 29 with recurrent TN, were included in a previous study (27). Of the 652 patients, 54 underwent a second treatment for recurrent TN. Of the 54 patients, 37 were available for long-term follow-up, with a mean follow-up interval of 3.8 years (range, 0.6–7.2). The characteristics of these 37 patients who had undergone repeat GKRS are summarized in Table 1.

Radiosurgery technique

After a preliminary evaluation by a radiation oncologist and neurosurgeon, the patient provided informed consent for treatment with GKRS. The patient was then treated by a team consisting of a neurosurgeon, radiation oncologist, and medical physicist. The neurosurgeon applied a Leksell Model G stereotactic head frame to the patient. The patient then underwent high-resolution, noncontrast-enhanced, stereotactic magnetic resonance imaging of the brain. One patient underwent treatment planning using computed tomography. Each patient's treatment plan was generated using the Leksell GammaPlan Treatment Planning System (Elekta). A 4-mm collimator was used in all but 2 patients, for whom concentric 4- and 8-mm collimators were used. The radiation dose was prescribed to the 100% isodose line for all patients. The treatment philosophy regarding the dose and isocenter location changed during the study period owing to the evolution of treatment practice. Patients treated early in our experience had the isocenter placed more proximally such that the 50% isodose line was tangential to the pons. Later in our experience, the initial isocenter was placed more distally at the pars triangularis. The repeat treatment isocenters were generally moved distally on the nerve, unless the initial treatment isocenter had been placed distally. In such cases, the second isocenter was moved closer to the brainstem to minimize overlap.

The mean initial prescription dose was 87.3 Gy (range, 80–90), with most patients receiving 90 Gy. The collimator output factor was 0.87 for the 4-mm collimator. The mean repeat treatment dose was 84.4 Gy (range, 60–90) using the same collimator output factor.

Follow-up

The patients were instructed to return for a follow-up examination 3–6 months after treatment, or sooner, if their pain had recurred. If pain control acceptable to the patient had been achieved, they were instructed to return on a need-only basis after the first post-treatment visit. Long-term follow-up data were obtained by telephone interview. The patients were excluded if they refused the telephone questionnaire or could not be interviewed by telephone. Deceased patients were included in the study if a spouse or caregiver with adequate knowledge of the patient's condition was available for questioning.

Efficacy scores

Pain relief was categorized as excellent, good, fair, or poor (EGFP). Excellent pain relief corresponded to complete pain relief without medications. Good pain relief corresponded to complete pain relief or minimal residual pain but still requiring medication. Fair pain relief corresponded to persistent symptoms, but with >50% pain relief with or without medications. Poor pain relief corresponded to persistent symptoms with <50% pain relief, independent of medication status. Treatment "success" was described in relationship to the outcome scores, in addition to the patient's subjective opinion determined by their satisfaction after the second GKRS.

Although recent publications on TN have more commonly used the Barrow Neurological Institute's classification for pain scores, we decided to continue using the EGFP classification to be consistent with previous publications from our institution. In addition, the EGFP classification is similar to the method described by Burchiel in a recent publication (28). According to the Burchiel classification, Grade I pain would be equivalent to an "excellent" outcome, Grade II pain would be equivalent to a "good" outcome, Grade IIIa and IIIb pain would both be included in the "fair" outcome, and Grade IV pain would be similar to a "poor" outcome in our series. One major difference between the two classifications is that <50% pain relief, regardless of medication status, was considered a poor outcome at our institution.

We also attempted to obtain the patients' subjective pain scores using an intensity scale from 0 to 10 at diagnosis and at follow-up to help classify their pain into the EGFP categories. Subjective pain intensity values were often recorded in the patients' charts from the initial consultation notes. Missing values were obtained by telephone interview. Changes in subjective pain intensities and the outcomes determined using the EGFP classification were used as indicators of treatment efficacy.

The interval to pain relief was recorded using the variables "time to complete pain relief" and "time to partial pain relief." Pain-free intervals were recorded as partial and complete pain-free intervals, because several patients experienced recurrence with a less severe intensity than before GKRS. If a patient experienced a period of complete pain relief, in addition to a period of partial pain relief, the partial pain-free interval recorded included the complete pain-free interval. The endpoint for a partial pain-free interval was the date at which <50% pain relief had occurred compared with the pre-treatment baseline pain level.

Dosimetry

The dosimetric variables were obtained retrospectively using the Leksell GammaPlan software and the archived treatment plans. We recorded variables that described the dose to

critical structures and the cumulative dose between the two treatments. Such variables included the dose administered at each treatment, the cumulative dose to the trigeminal nerve, the dose to the pons surface with each treatment, the cumulative dose to the pons surface, the dose to the trigeminal ganglion with each treatment, the cumulative dose to the trigeminal ganglion, the dose to the dorsal root entry zone (DREZ) with each treatment, and the cumulative DREZ dose.

The DREZ was defined radiographically as the point at which the center of the nerve intersected the brainstem. The pons dose was defined as the closest point on the pons orthogonal to the isocenter to estimate the maximal dose at the surface of the pons. The isocenter distances were recorded from the pons and the trigeminal ganglion as variables to describe the isocenter location along the trigeminal nerve. We used the point at which the nerve crossed the petrous dura as a landmark for the distal portion of the trigeminal nerve (29). Figure 1 shows the landmarks and method on an axial magnetic resonance imaging slice captured from the GammaPlan.

Electronic medical records were used to obtain the demographic data, medical history, medications at treatment, and other relevant information. Other data were acquired from the telephone interview. Missing data are indicated by a sample size <37.

Statistical analysis

The reported *p* values are from chi-square contingency table analyses. In addition to the previously defined pain-free intervals, the interval to pain recurrence for those who never had complete pain relief was defined as 1 day for the statistical analysis. The same method was used when defining the interval to pain recurrence from partial pain relief. We used the Kaplan-Meier method to calculate the interval-to-pain recurrence curves.

RESULTS

Efficacy

Of the 54 patients who had undergone repeat GKRS for recurrent TN, 37 had sufficient data to determine the outcomes. Overall, 17 patients (46%) had excellent pain relief, 9 (24%) had good pain relief, 5 (14%) had fair pain relief, and 6 (16%) had poor pain relief. Thus, 31 patients (84%) experienced >50% pain relief with repeat GKRS. The mean interval to complete pain relief was 10.5 weeks, although this interval ranged from 1 day to 78 weeks. Three patients experienced an abnormally long period to complete pain relief of 52 (*n* = 2) and 78 weeks. Excluding those outliers who likely experienced spontaneous remission, the mean interval to complete pain relief was 3.4 weeks. Figures 2 and 3 show the Kaplan-Meier curves for the pain-free intervals for complete and partial pain relief.

Toxicity

In the present analysis, any abnormal facial sensation, including numbness, parasthesia, and hypesthesia, was classified as treatment-related "toxicity." To determine the toxicity of repeat GKRS, the patients were asked about the presence of numbness or abnormal facial sensations after repeat GKRS. They were also questioned about any other bothersome toxicities or surgical procedures that these toxicities might have brought about. Of the 37 patients, 21 (57%) had some degree of trigeminal nerve dysfunction after repeat GKRS. Of the 26 patients who had had no numbness before the second GKRS, 10 (38%) had developed numbness after the repeat procedure. Of the 11 patients with pre-existing numbness before repeat GKRS, 3 (27%) experienced worsening of this numbness after the second procedure. One patient with mild numbness after the first procedure experienced severe, bothersome numbness after repeat GKRS. This patient described the nerve

dysfunction as more bothersome than the pain from TN. The patient had possibly experienced anesthesia dolorosa, although his symptoms were “bothersome numbness,” not painful or burning facial numbness. One patient with worsened numbness experienced corneal dryness that required tarsorrhaphy. The patient requiring tarsorrhaphy claimed that the dryness and the subsequent procedure were preferable to the pain from TN.

An analysis was also performed to determine whether the presence of numbness correlated with the likelihood of a better or worse outcome. Of the 21 patients who had experienced some degree of numbness, 14 (67%) had an excellent outcome ($n = 36$, $p = .0057$). In addition, 21 (100%) of 21 patients experiencing numbness had >50% pain relief, and 9 (60%) of 15 patients experiencing no numbness had >50% pain relief ($n = 36$, $p = .0015$). None of 6 patients with poor outcomes had sensory disturbances after GKRS.

Dosimetric factors

Of the 37 patients, 36 had received a prescription dose >70 Gy at repeat GKRS. The remaining patient had received 60 Gy in the retreatment setting. Most patients had received 80–90 Gy. An analysis was performed to determine whether a dose response was present regarding the prescription dose in the present series. No dose response was detected in our analysis.

Using the GammaPlan treatment planning system, we calculated several dosimetric variables. The results are summarized in Table 2. A statistical analysis was subsequently performed to determine whether a correlation existed between any of the calculated dosimetric variables and the treatment efficacy and toxicity. The results of the correlation of the dosimetric variables and outcomes are summarized in Table 3. The DREZ dose at repeat treatment was predictive of both efficacy and toxicity. The median DREZ dose at repeat treatment was 26.6 Gy. Of the 19 patients receiving 26.6 Gy to the DREZ, 6 (32%) experienced an excellent outcome. In contrast, 11 (61%) of the 18 patients who had received >26.6 Gy experienced an excellent outcome ($p = .0716$).

The most significant predictive factor of numbness in our series was the cumulative pons surface dose. The incidence of numbness was 78% in patients who had received >108.5 Gy (the median pons surface dose), but it was only 39% in patients who had received less than the median dose ($p = .018$). The DREZ dose at repeat treatment was less predictive of toxicity. Of the 19 patients receiving <26.6 Gy, 9 (44%) experienced numbness, and 70% of the patients receiving >26.6 Gy experienced numbness ($p = .158$). The cumulative DREZ dose was also predictive of the occurrence of toxicity. The median cumulative DREZ dose for the two GKRS procedures was 84.3 Gy. Of the 18 patients receiving a total dose of 84.3 Gy, 13 (72%) experienced numbness. In contrast, only 8 (44%) of 18 patients receiving <84.3 Gy experienced numbness after the second GKRS ($p = .091$).

The isocenter location along the nerve did not appear to have predictive value for our outcome measures. Neither the isocenter distance from the pons nor the isocenter distance to the petrous dura predicted for treatment efficacy or toxicity in our statistical analysis.

Patient-related factors

To determine the patient-related risk factors that predicted for treatment success or failure, we attempted to compare the efficacy and toxicity outcomes in subsets of our treatment population. Our series included 9 patients with atypical TN, as defined by Burchiel’s classification. Patients with atypical TN in our series appeared to have an outcome similar to that of patients with a typical presentation. Of the patients with TN with atypical features, 44% had excellent outcomes compared with 46% of patients with typical pain and excellent

outcomes. In addition, 77% of patients with components of atypical pain had >50% pain relief compared with 85% of patients with typical pain. Patients with atypical pain experienced numbness in 55% of the cases, and patients with typical pain experienced numbness in 37% of the cases. Our series included 4 patients with multiple sclerosis, 1 of whom experienced an excellent outcome. Of the remaining multiple sclerosis patients, 1 each had a good, fair, and poor outcome.

Patients with no previous surgery experienced better outcomes than those who had undergone procedures before they opted for GKRS. Of the 23 patients who had not undergone previous surgical intervention, 12 (56%) experienced an excellent outcome compared with 4 (29%) of the 14 patients who had undergone a previous surgery ($p = .098$). Age, gender, pain distribution, smoking history, hypertension, current medication use, and a history of diabetes did not correlate with efficacy or toxicity.

DISCUSSION

Patient outcomes

Several institutions have reported on the use of repeat GKRS for recurrent TN as summarized in Table 4. The data for repeat GKRS for TN have been limited by the small number of patients, limited follow-up time, and heterogeneity of treatment philosophies. A total of 308 patients who had undergone repeat GKRS have been reported to date (17–25, 30). However, the doses used for repeat treatment have been inconsistent, ranging from 40 Gy to >80 Gy in various series (18, 19). The target location has also varied, from the use of the same isocenter from the previous treatment to a more anterior location (18, 19, 25, 26). As a result of this heterogeneity, the published data have been difficult to interpret regarding the prognostic factors for treatment success and toxicity. Moreover, the largest series of repeat GKRS for TN had a mean follow-up time of only 15 months (20). In our retrospective analysis, the significance of the isocenter location and dose of the second treatment were analyzed. Additionally, the determination of the risk factors for the treatment response and improved quality of life were considered. Although the numbers in our series were also limited, the median follow-up of 3.8 years in our series was among the longest in published studies for such a series.

The results of the present study have demonstrated a positive correlation between patients who experienced post-therapy numbness and patients who ultimately achieved both a complete response and an improved quality of life. This correlation between toxicity and efficacy has been previously reported in patients treated with GKRS. Pollock *et al.* (12) described sensory disturbance in 37% of 117 patients treated with definitive GKRS at the Mayo clinic, with 12% of the patients describing clinically bothersome numbness. The Mayo group later described a greater rate of pain relief for patients treated with 90 Gy vs. 70 Gy and also noted an increased risk of trigeminal nerve dysfunction in the higher dose cohort (9). The collimator output factor used in that study was 0.80, possibly increasing the effective dose to the nerve compared with more recent publications. Multiple series have now reported that patients who experienced sensory dysfunction were also more likely to be pain free (30, 31). Although the paradigm of treatment for TN with GKRS had previously been to maximize treatment efficacy while minimizing numbness, current and previous data would suggest that treating to the threshold of some clinical numbness predicts for treatment efficacy among patients with recurrent TN.

Isocenter location

The optimal location of the isocenter for the initial treatment of TN with GKRS has been somewhat controversial. Kondziolka *et al.* (2) targeted the proximal nerve under the

assumption that oligodendrocytes is more sensitive to radiation than the Schwann cells and are located near the DREZ. They found an improved outcome with doses of 70 Gy. A controlled comparison between treatment cohorts in France and Belgium showed that an increased nerve root dose correlated with greater numbness and greater pain relief (31). Although our series failed to reach statistical significance in relating the cumulative DREZ dose to a positive outcome, a trend was seen, suggesting that this relationship in the repeat treatment setting. In selected cases, delivering greater doses close to the DREZ would be difficult because the anatomic course of the nerve is in close proximity to the pons within the prepontine cistern. Restricting the dose in these cases to the surface of the pons is a challenge, requiring placement of the isocenter more distally along the nerve. Regis *et al.* (7) reported an excellent rate of improvement in quality of life and a low rate of toxicity with distal isocenter placement for the first GKRS. A more distally placed isocenter at the first application of GKRS in such cases would allow a future application to be delivered more proximally, where the change from oligodendrocytes to Schwann cells at the DREZ makes this portion of the nerve more radiation sensitive. If one were forced to deliver a lower dose at repeat treatment because of pontine surface dose constraints, the DREZ would be the logical location for delivery while maintaining a reasonable chance of success.

Toxicity

The toxicity seen in the present series was relatively mild and comparable to that of other studies, even considering that higher doses were used for both the first and the second treatments. One patient experienced corneal dryness, a toxicity that required temporary surgical correction. Corneal dryness has been reported in the published data to be related to the brainstem volume irradiated and is often preceded by V1 hypesthesia (32). The only case of significant toxicity in the present series was 1 patient with bothersome numbness or questionable anesthesia dolorosa, although this patient did not describe pain when completing the questionnaire. The cumulative pons surface dose was the major dosimetric factor that predicted for trigeminal dysfunction in our series. Previous published series have also reported that the brainstem dose is predictive of the development of numbness (6). Of 21 patients in the present study with trigeminal dysfunction, 20 qualitatively rated their numbness as not bothersome. One question that arises given the correlation of better quality of life with some degree of numbness is whether non-bothersome numbness should be considered an adverse event. Among surgeons who perform radiofrequency ablation as a definitive modality for TN, some degree of clinical numbness has often been considered a desired outcome. However, traditionally, in the gamma knife data for TN, numbness has been equated with toxicity. The patients included in the present series were always counseled regarding the risk of complications when undergoing a second GKRS for TN. Patients who were apprehensive about the potential toxicities were generally given a lower radiation dose at repeat treatment.

Study limitations

The present series had some limitations. First, the nature of a retrospective study is less than ideal when considering data analysis for statistical and clinical significance. During the treatment period, the repeat treatment philosophy changed on the basis of the published data. Although this allowed for different treatment strategies to be compared with each other, it limited the interpretation of the data. In addition, the patient population in our study was quite heterogeneous. Nine patients with “atypical features,” in addition to 4 patients with multiple sclerosis were included in our data analysis. Multivariate analysis showed that these patients were not significantly different from the typical TN patients during the follow-up period. Historically, however, such patients have developed recurrence more quickly, and a longer follow-up period would likely show the same results in our study. An ideal study would separate typical or Type I TN from all others and provide a prospective dosimetric

analysis. This scenario would likely require a multi-institutional study to increase the treatment population and provide more power for the study and, subsequently, greater statistical significance.

CONCLUSION

Repeat GKRS can be used to treat TN with the understanding that a second radiosurgical procedure increases the risk of significant numbness. In addition, the results of the present series demonstrated a trend toward better treatment outcomes when a higher dose to the DREZ was used at repeat treatment. The data have suggested that greater rates of numbness should be acceptable to obtain optimal pain relief. As with any surgical procedure, patients should be counseled regarding the risks and benefits of a second GKRS for TN. Specifically, patients and physicians might wish to accept more numbness in exchange for adequate pain control at repeat treatment, consistent with other ablative surgical techniques for TN.

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Fig. 1.

Axial slice magnetic resonance image showing 50% and 95% isodose curves from gamma knife radiosurgery plan using single 4-mm shot. Crosshairs placed at dorsal root entry zone to calculate point dose. "Measure" tool from GammaPlan software calculated distance from shot to pons and gasserian ganglion.

Fig. 2.
Kaplan-Meier curve showing survival time with some degree of pain relief improved from pretreatment intensity.

Fig. 3.
Kaplan-Meier curve showing survival time with complete pain relief.

Table 1**Demographics**

Demographic	Value
Gender	
Male	17 (46)
Female	20 (54)
Pain side	
Right	20 (54)
Left	17 (46)
Distribution	
V1	2 (5)
V1, V2	1 (3)
V1, V2, V3	6 (16)
V2	15 (41)
V2, V3	9 (24)
V3	4 (11)
Pain type	
Typical	29 (78)
Atypical	8 (22)
Comorbidities	
Multiple sclerosis	4 (11)
Hypertension	16 (43)
Diabetes	3 (8)
Autoimmune disease	
Smoker	10 (27)
Never smoked	15 (41)
Former smoker	12 (32)
Previous surgical procedures	13 (35)
Surgical procedures (<i>n</i>)	
0	24 (65)
1 or 2	9 (24)
3	4 (11)
Surgical procedures between GK treatments	2 (5)
Procedure before first GKRS	
Microvascular decompression	6 (16)
Rhizotomy	10 (27)
Nerve block	5 (14)
Mean dose at first GKRS (Gy)	87.3
Mean dose at second GKRS (Gy)	84.2
Mean total dose (Gy)	171.5
Mean interval between GKRS (y)	1.3
Mean duration of pain before second GKRS (y)	1.7

Abbreviations: GK = gamma knife; GKRS = gamma knife stereotactic radiosurgery.

Data presented as numbers of patients, with percentages in parentheses, unless otherwise noted.

Table 2

Dosimetric characteristics of gamma knife stereotactic radiosurgery

Variable	First GKRS	Second GKRS	Cumulative
Mean isocenter distance from pons	2.4	3.2	
Mean isocenter distance from petrous dura	4.7	3.7	
Mean pons surface dose	46.8	59.1	105.9
Mean dose of nerve at petrous dura	29.5	24.4	43.5
Mean DREZ dose	46.3	34.3	80.6

Abbreviations: GKRS = gamma knife stereotactic radiosurgery; DREZ = dorsal root entry zone.

Table 3
Efficacy of second gamma knife stereotactic radiosurgery according to dosimetric characteristics

	Second GKRS (%)			Cumulative (%)	
	Excellent	Good, fair, poor	Toxicity	Excellent	Good, fair, poor
Dose < 85 Gy	48	52			
Dose > 90 Gy	43	57			
Dose to petrous dura greater than median	44	56	50	50	50
Dose to petrous dura less than median	47	53	67	42	58
Dose to pons greater than median	44	56	61	56	44
Dose to pons less than median	47	53	56	37	63
DREZ dose greater than median	61	39	71	47	53
DREZ dose less than median	32	68	47	44	56

Abbreviations as in Table 2.

Table 4

Published series of repeat gamma knife stereotactic radiosurgery for trigeminal neuralgia

Investigator	Patients (n)	Follow-up (mo)	Previous surgery (%)	GK dose (Gy)			Outcome (%)			Any toxicity (%)	Recurrence (%)
				First	Second	Excellent	Good	Fair	Poor		
Pollock <i>et al.</i> (17), 2000	10	15 (mean)	10	70	88	80	10	0	10	80	11
Hasegawa <i>et al.</i> (18), 2002	27	20.4 (median)	82	76	64	19	30	37	15	13	17
Shetter <i>et al.</i> (19), 2002	19	13.5 (mean)	NA	78	46	53	32	15	0	42	NA
Brisman (20), 2003	45	15 (mean)	51	75	40	22	20	20	38	13	24
Herman <i>et al.</i> (21), 2004	18	24.5 (median)	28	75	70	45	33	0	22	11	17
Pollock <i>et al.</i> (22), 2005	19	24 (median)	95	82	76	74	5	16	5	58	21
Zhang <i>et al.</i> (23), 2005	40	28 (median)	48	75	40	28	18	20	37	13	NA
Urgosik <i>et al.</i> (26), 2005	19	36 (median)	NA	70–80	70–80	58	21	11	11	32	5
Huang 2006 (33)	28	43 (median)	39	79	52	43	18	7	32	36	32
Wang <i>et al.</i> (24), 2008	34	21.6 (mean)	62	73	71	53	32	12	3	12	9
Gellner <i>et al.</i> (25), 2008	22	64.5 (mean)	50	75	74	76	24	0	0	74	27
Dvorak <i>et al.</i> (30), 2009	27	20 (median)	25	80	45	29	32	25	14	29	NA
Present study, 2009	37	48 (median)	38	87	84	46	24	14	16	57	19

Abbreviations: GK = gamma knife; NA = not available.