Stereotactic radiosurgery for trigeminal pain secondary to recurrent malignant skull base tumors

Jack Phan, MD, PhD,¹ Courtney Pollard III, MD, PhD,¹ Paul D. Brown, MD,⁶
Nandita Guha-Thakurta, MD,⁵ Adam S. Garden, MD,¹ David I. Rosenthal, MD,¹
Clifton D. Fuller, MD, PhD,¹ Steven J. Frank, MD,¹ G. Brandon Gunn, MD,¹
William H. Morrison, MD,¹ Jennifer C. Ho, MD,¹ Jing Li, MD, PhD,¹ Amol J. Ghia, MD,¹
James N. Yang, PhD,⁴ Dershan Luo, PhD,⁴ He C. Wang, PhD,⁴ Shirley Y. Su, MD,³
Shaan M. Raza, MD,² Paul W. Gidley, MD,³ Ehab Y. Hanna, MD,³ and Franco DeMonte, MD²

Departments of ¹Radiation Oncology, ²Neurosurgery, ³Head and Neck Surgery, ⁴Radiation Physics, and ⁵Diagnostic Radiology, University of Texas MD Anderson Cancer Center, Houston, Texas; and ⁶Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

OBJECTIVE The objective of this study was to assess outcomes after Gamma Knife radiosurgery (GKRS) re-irradiation for palliation of patients with trigeminal pain secondary to recurrent malignant skull base tumors.

METHODS From 2009 to 2016, 26 patients who had previously undergone radiation treatment to the head and neck received GKRS for palliation of trigeminal neuropathic pain secondary to recurrence of malignant skull base tumors. Twenty-two patients received single-fraction GKRS to a median dose of 17 Gy (range 15–20 Gy) prescribed to the 50% isodose line (range 43%–55%). Four patients received fractionated Gamma Knife Extend therapy to a median dose of 24 Gy in 3 fractions (range 21–27 Gy) prescribed to the 50% isodose line (range 45%–50%). Those with at least a 3-month follow-up were assessed for symptom palliation. Self-reported pain was evaluated by the numeric rating scale (NRS) and MD Anderson Symptom Inventory–Head and Neck (MDASI-HN) pain score. Frequency of as-needed (PRN) analgesic use and opioid requirement were also assessed. Baseline opioid dose was reported as a fentanyl-equivalent dose (FED) and PRN for breakthrough pain use as oral morphine-equivalent dose (OMED). The chi-square and Student t-tests were used to determine differences before and after GKRS.

RESULTS Seven patients (29%) were excluded due to local disease progression. Two experienced progression at the first follow-up, and 5 had local recurrence from disease outside the GKRS volume. Nineteen patients were assessed for symptom palliation with a median follow-up duration of 10.4 months (range 3.0–34.4 months). At 3 months after GKRS, the NRS scores (n = 19) decreased from 4.65 ± 3.45 to 1.47 ± 2.11 ($p < 0.001$); MDASI-HN pain scores (n = 13) decreased from 5.02 ± 1.68 to 2.02 ± 1.54 ($p < 0.01$); scheduled FED (n = 19) decreased from 62.4 ± 102.1 to 27.9 ± 45.5 mcg/hr ($p < 0.01$); PRN OMED (n = 19) decreased from 43.9 ± 77.5 to 10.9 ± 20.8 mg/day ($p = 0.02$); and frequency of any PRN analgesic use (n = 19) decreased from 0.49 ± 0.55 to 1.33 ± 0.90 per day ($p = 0.08$). At 6 months after GKRS, 9 (56%) of 16 patients reported being pain free (NRS score 0), with 6 (67%) of the 9 being both pain free and not requiring analgesic medications. One patient treated early in our experience developed a temporary increase in trigeminal pain 3–4 days after GKRS requiring hospitalization. All subsequently treated patients were given a single dose of intravenous steroids immediately after GKRS followed by a 2–3-week oral steroid taper. No further cases of increased or new pain after treatment were observed after this intervention.

CONCLUSIONS GKRS for palliation of trigeminal pain secondary to recurrent malignant skull base tumors demonstrated a significant decrease in patient-reported pain and opioid requirement. Additional patients and a longer follow-up duration are needed to assess durability of symptom relief and local control.

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KEYWORDS Gamma Knife radiosurgery; stereotactic radiosurgery; trigeminal neuralgia; skull base tumor; palliation; pain; oncology

ABBREVIATIONS BNI = Barrow Neurological Institute; FED = fentanyl-equivalent dose; GKE = Gamma Knife Extend; GKRS = Gamma Knife radiosurgery; MDACC = MD Anderson Cancer Center; MDASI-HN = MD Anderson Symptom Inventory–Head and Neck; NRS = numeric rating scale; OMED = oral morphine-equivalent dose; PRN = as needed; SRS = stereotactic radiosurgery; TN = trigeminal neuralgia.

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TRIGEMINAL neuralgia (TN) is characterized by intermittent attacks of lancinating unilateral facial pain. The majority of cases are primary or idiopathic as a result of vascular compression of the trigeminal nerve. TN secondary to tumors represents 3%–13% of cases,⁷ and is frequently due to benign tumors such as meningiomas and schwannomas compressing the nerve root entry zone or trigeminal ganglion and peripheral nerves within the cavernous sinus.^{8,18} A less commonly reported phenomenon is trigeminal neuropathic pain (secondary TN) resulting from head and neck malignant tumors invading the skull base, often presenting with direct nerve invasion and producing a constant burning-type pain.^{3,6,17}

Medical therapy and percutaneous techniques such as radiofrequency rhizotomy can provide initial but not durable pain relief because the underlying tumor is not addressed.^{4,8} Radical resection of tumor can provide durable symptom relief and tumor control but complete resection of many skull base tumors is not possible and carries the risks of CSF leakage, hematomas, infarctions, and cranial nerve deficits.^{2,4,11} Gamma Knife radiosurgery (GKRS) has emerged as a noninvasive surgical option for treatment of primary and secondary TN by delivering high doses of precise radiation to the trigeminal nerve or tumor.

Local control after radiotherapy for head and neck cutaneous squamous cell carcinomas is encouraging and approaches 80%–90% in patients without perineural invasion.^{16,36} In those with perineural disease, the rates of skull base perineural recurrence after definitive radiotherapy can be as high as 40%–60%, with cutaneous squamous cell carcinoma or adenoid cystic carcinoma having a proclivity for skull base recurrence.^{13,21,24,32} In addition to the poor prognosis for these tumors,^{5,12} symptom burden in these patients can be debilitating. Those with trigeminal pain often require high doses of narcotics for pain control and their opioid requirement is progressive.^{8,31}

Several reports have demonstrated the effectiveness of GKRS for the treatment of secondary TN caused by benign tumors, with documented improvement in pain relief in 45%–70% of patients.^{25,33} The published outcome data on the role of GKRS re-irradiation for patients with recurrent malignant skull base tumors is limited to its role as a boost to supplement external beam re-irradiation or focal treatment of gross residual disease in the skull base after surgery to improve local control.^{23,34} The role of GKRS for palliation of trigeminal pain in patients with recurrent malignant tumors of the head and neck has not, to our knowledge, previously been reported. The purpose of this study was to assess the outcomes of patients who previously had undergone radiation treatment and experienced malignant skull base tumor recurrences causing trigeminal pain, treated with single-fraction GKRS or fractionated stereotactic radiosurgery (SRS) using the Gamma Knife Extend (GKE).

Methods

Study Population

This study was approved by the IRB of the MD Anderson Cancer Center (MDACC). Patients with recurrent skull base tumors after prior head and neck radiotherapy subse-

quently treated with GKRS in the Department of Radiation Oncology at MDACC between June 2009 and March 2016 formed the initial parent cohort. Patients treated nonpalliatively for local control (i.e., isolated retropharyngeal recurrence), as a boost supplement to external beam irradiation, for benign skull base tumors, or with less than 3 months of follow-up were excluded from further analysis. The medical records of 26 eligible patients with tumor-associated trigeminal facial pain were retrospectively reviewed for demographics, prior radiation treatment details, pre- and posttreatment MRI, radiosurgery planning details, and clinical status. Beginning in 2013, a prospective head and neck re-irradiation database including patient-reported outcome data was established and maintained throughout this period.

Self-Assessed Pain Score, Analgesic Requirement, and Opioid Use

Self-reported pain assessment for each patient was determined using the numeric rating scale (NRS),¹⁴ the MD Anderson Symptom Inventory–Head and Neck (MDASI-HN) pain score,^{28,29} and the Barrow Neurological Institute (BNI) pain intensity score.²⁷ The NRS is a self-reported pain intensity scale widely used in the clinical setting to assess “real-time” pain. Scores range from 0 to 10, in which 0 is “no pain” and 10 represents “the most severe pain.” For patients prospectively enrolled in our head and neck re-irradiation registry (n = 13), an additional method of determining self-assessed pain was evaluated using the pain item of the MDASI-HN, which is a validated patient-reported symptom burden assessment questionnaire consisting of 22 core items and 6 head- and neck-specific items rated “in the last 24 hours” on a scale from 0 (“not present”) to 10 (“as bad as you can imagine”).²⁸ BNI pain criteria were defined as: grade I (no pain and no medications required), grade II (occasional pain with no medications required), grade IIIa (no pain with medication), grade IIIb (tolerable pain adequately controlled with medication), and Grades IV and V (no pain relief or not adequately controlled with medication). For this study, pain response was defined as “excellent” if the patient reported being pain free or with occasional tolerable pain and off analgesics (BNI score I or II); or “good” if pain free on analgesics (pain free or with occasional tolerable pain on analgesics).

The frequencies of as-needed (PRN) analgesic and opioid use were obtained via clinical documentation and medication records. The frequency of PRN nonopioid analgesic use was recorded as daily frequency (1/n); therefore, larger numbers indicate lower frequency of daily PRN analgesic use. The daily baseline opioid requirement was recorded and translated to corresponding fentanyl-equivalent dose (FED; in mcg) per hour. PRN opioid medication dose was recorded and converted to an oral morphine-equivalent dose (OMED). An “excellent response” was defined as pain free and completely off any analgesic. A “good response” was defined as pain free on analgesics. Facial pain outcomes were classified as “excellent” (pain free without any further treatment after SRS and not requiring any medication for TN pain), “good” (pain free without further treatment but remained on medication for pain), “fair” (facial pain improved but not completely alleviated with the same

or reduced pain meds), and “poor” (facial pain did not improve or became worse). If pain improved but recurred in the absence of tumor recurrence, the pain score was based on last follow-up prior to documented recurrence. Patients were followed at regular intervals of 3–6 months, 6–12 months, and 1–2 years. The pretreatment NRS score was obtained from the most recent clinical note prior to GKRS. NRS score, MDASI-HN pain score, and analgesic use were obtained during each follow-up visit. Initial follow-up was based on clinical evaluation at regular intervals, i.e., 3 months, 6 months, and 1 year after treatment. For patients completing the MDASI-HN, questionnaires were completed either by the patient and mailed in, by in-person interview during clinic visit, or by telephone interview for patients unable to come in for follow-up. Clinical evaluations were made by our medical research team during follow-up and every clinical evaluation made by our team was prospectively collected in the database.

Treatment Planning and Patient Follow-Up

All patients were treated with the Leksell Gamma Knife Perfexion model (Elekta). In all cases, the target of treatment was the tumor. The trigeminal nerve and/or root was not specifically targeted for ablation as is typically performed for TN. The primary goal of treatment was to delay local disease progression with a secondary goal of achieving symptom relief. Treatment plans were performed using the Leksell GammaPlan treatment planning system by the treatment team consisting of a radiation oncologist, neurosurgeon, and medical physicist. A diagnostic T1-weighted MR image with contrast was obtained within 4 weeks prior to treatment. For single-session GKRS, a head frame was affixed to the patient's skull with 4 pins on the day of treatment and volumetric contrast-enhanced MRI scans with 1-mm slice thickness were obtained as previously described^{30,35} (Fig. 1). For fractionated GKRS, the GKE system was used, which is a noninvasive fixation system that consisted of a stereotactic frame attached to the patient via a vacuum-sealed mouthpiece (Fig. 2). One day prior to the first treatment, the GKE frame was placed, and a non-contrast-enhanced CT scan with 1-mm slice thickness was obtained and coregistered to a volumetric contrast-enhanced MR image. On each day of treatment, a verification CT scan was performed and fused to the planning image set to verify setup consistency.

All patients were evaluated by the multidisciplinary team, including neurosurgeons, skull base surgeons, medical oncologists, and radiation oncologists. The goal of treatment was to cover the entire tumor with the prescribed dose. Target delineation was determined in collaboration with the treating radiation oncologist, neurosurgeon, and neuroradiologist. Treatment dose was based on the size, extent, and location of tumor, slightly modified from the data determined by the Radiation Therapy Oncology Group 90–05 study for intracranial metastases. For smaller tumors < 6 cm³, the goal was a prescribed dose of 18–21 Gy to the 50% isodose line. For tumors > 6 cm³ and/or in instances in which the dose constraint of a critical structure was exceeded, the prescribed dose was lowered to 15–17 Gy to the 50% isodose line. For tumors larger than 12 cm³, the total dose was increased and treatment fractionated

over 3 sessions to reduce neurological toxicity risk. The critical structure goals used for single-session SRS were < 8 Gy (optic apparatus), < 12 Gy (brainstem), and < 9 Gy (cochlea). The dose constraints used for 3-fraction GKE were < 20 Gy (optic apparatus), < 23 Gy (brainstem), and 22 Gy (cochlea). Patients were examined approximately 4–10 weeks after completion of SRS and then every 2–4 months with repeat imaging, including head and neck CT and/or MRI of the orbit and brain for year-1 follow-up.

Data Analysis

Patient outcomes were performed using descriptive statistics. Disease progression was defined by a radiographic increase in tumor volume from the pretreatment imaging. A complete/near-complete response was > 80% reduction in tumor volume from the pretreatment imaging. A partial response was defined as < 80% decrease in tumor volume from the pretreatment imaging. Stable disease was defined as no/minimal change in tumor volume from the pretreatment imaging. These definitions were based on findings from the reading neuroradiologist and confirmed independently by a second neuroradiologist. The clinical outcomes assessed were overall survival and local control and calculated using the Kaplan-Meier method with prognostic factors determined by the log-rank test. Side effects from treatment were graded using the Common Toxicity Criteria for Adverse Events (version 4.03). The Student t-test was used to compare mean values of NRS, MDASI-HN pain score, FED, OMED, and frequency of analgesic use; p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (version 21, IBM Corp.) and JMP (version 10, SAS Institute).

Results

Patient and Tumor Characteristics

Between 2009 and 2016, 26 consecutive patients with recurrent skull base malignant tumors were treated with GKRS to palliate tumor-associated trigeminal pain. The patient and tumor characteristics are shown in Table 1. The median age at diagnosis of recurrence was 56 years (range 35–81 years). Squamous cell carcinoma (n = 9) and adenoid cystic carcinoma (n = 10) represented the most common histologies (73% combined), with other histologies consisting of nasopharynx carcinoma (n = 3), adenocarcinoma (n = 2), acinic cell carcinoma (n = 1), and Hurthle cell carcinoma (n = 1). More than half (54%) of the patients had an original primary site involving the skin/scalp or salivary glands (n = 14; 54%). Pain distribution commonly involved multiple cranial nerve V branches (69%), with single branch involvement most common in V3 (15%), followed by V2 (12%), and V1 (4%). Sixteen patients (62%) experienced concomitant facial paresthesia. Fifty-four percent of treatment targets (14 of 26) involved the cavernous sinus. The median dose for GKRS patients (n = 22) was 17 Gy (range 15–20 Gy) prescribed to the 50% (median) isodose line (range 43%–55%). The median dose for GKE patients (n = 4) was 24 Gy (range 21–27 Gy) prescribed to the 50% isodose line (except for 1 patient who was prescribed to the 46% isodose line). The median volumes for patients

FIG. 1. Images from a patient treated with single-fraction GKRS for TN. This patient was previously treated for adenoid cystic carcinoma of the floor of the mouth. The patient presented with right-sided facial pain along the V2 and V3 distribution and was found to have recurrent tumor involving the skull base. **A:** Treatment-planning T1-weighted postcontrast MR image showing tumor involving Meckel's cave (arrow). **B:** Contrast enhancement of trigeminal nerve disease at the level of the prepontine cistern (arrows). **C:** GKRS treatment plan. The patient was treated at 16 Gy in 1 fraction to the 50% isodose line. The brainstem (turquoise contour) does not receive any high-dose radiation. **D:** At 6 months, pain level decreased from 7/10 to 1/10; the hydromorphone requirement decreased from 2 mg every 2 hours to 2 mg twice daily PRN. Posttreatment MRI showed no residual contrast enhancement in Meckel's cave (dashed circle). Figure is available in color online only.

treated with GKRS and GKE were 4.2 cm³ (range 1.9–12.4 cm³) and 9.7 cm³ (range 4.9–23.7 cm³), respectively.

Clinical Outcomes

Seven patients (27%) demonstrated disease progression at first follow-up (n = 2) or recurrence within 3 months after an initial response on imaging (n = 5; Table 2). Those with disease progression or recurrence experienced worsening of clinical symptoms prior to imaging confirmation. The median time to local recurrence was 2.8 months (range 1.2–6.8 months). All 7 patients with local progression/recurrence died and this accounted for the 7 deaths observed in this study. Of the 19 patients without disease progression or recurrence, 4 had a complete/near complete

response, 9 had a partial response, and 6 had stable disease. The median follow-up time was 10.4 months (range 3.0–34.4 months). The median time for radiographic treatment response was 6.3 months (4.4–8.1 months), with 13 patients showing stable disease on the first follow-up scan followed by continued evidence of treatment response on subsequent serial MRI. Treatment response data are summarized in Table 2.

Early in our experience, 1 patient developed an acute toxicity presenting as an increase in neuropathic pain 3–4 days after GKRS requiring hospitalization. Subsequent patients were given intravenous steroids immediately after the procedure followed by a 2-week oral steroid taper. No further cases of increased or new acute pain were observed. There were no notable late treatment effects. Three

FIG. 2. Images obtained in a patient treated with multifraction GKE for salivary gland carcinoma recurrent to the right skull base after presenting with right facial numbness and pain. **A:** Extensive tumor involvement of the cavernous sinus and Meckel's cave with invasion into the right brainstem (*dashed line* delineates superior to inferior extent of tumor) precluded use of single-fraction GKRS. **B:** GKE stereotactic head frame utilizing a noninvasive fixation system attached to the patient via a vacuum-sealed mouthpiece (*asterisk*). **C:** Volumetric contrast-enhanced treatment-planning MRI. The patient was treated at 21 Gy in 3 fractions to the 46% isodose line. The volume of uninvolved brainstem (*pink contour*) that received 16 Gy was kept below 0.3 cm³. **D:** At 6 months after treatment, pain was reduced from 4/10 on morphine sulfate controlled-release and oxycodone and gabapentin to 0/10 on gabapentin alone. MRI showed stable enhancement at the level of the right Meckel's cave (*dashed arrow*) with decreased enhancement and compression of the right lateral brainstem (*dashed oval*). Figure is available in color online only.

patients had preexisting temporal lobe necrosis from their initial radiotherapy course, with no progression of temporal lobe necrosis after GKRS.

Symptom Palliation

Response in pain relief and analgesic use are illustrated in Table 3. Between 3 and 6 months, 15 (79%) of 19 patients reported complete pain relief (BNI score I or IIIa), 3 (16%) of 19 patients reported partial pain relief (BNI score II or IIIb), and 1 patient (5%) reported no pain relief (BNI score IV). This patient had untreated disease outside the radiosurgical field and was later found to have evidence of

local recurrence at 4.8 months. Between 6 and 12 months follow-up, 13 (81%) of 16 patients reported complete pain relief and 3 (19%) of 16 patients reported partial pain relief. At more than 1 year of follow-up, 8 (100%) of 8 patients reported complete pain relief. Of 13 patients with complete pain relief between 6 and 12 months, 9 had an “excellent response” and were no longer taking analgesics. Of the 8 patients with complete pain relief at more than 1 year, 6 were no longer taking analgesics. The median time to being completely pain free was 4.6 months (range 3.1–6.9 months). The median initial response time for some pain relief was 2.6 months (range 2.1–4.6 months).

Patient-reported mean NRS scores decreased to 1.47 at

TABLE 1. Patient and treatment characteristics

Variable	Value
No. of patients	26
Age (yrs)	
Median (range)	56 (35–81)
Sex, no. (%)	
Male	16 (62)
Primary site, no. (%)	
Scalp/skin	6 (23)
Major salivary gland	4 (15)
Minor salivary gland	4 (15)
Oral cavity	4 (15)
Nasopharynx	3 (12)
Paranasal sinus	3 (12)
Orbit	1 (4)
Thyroid	1 (4)
Histology, no. (%)	
Adenoid cystic carcinoma	10 (38)
Squamous cell carcinoma	9 (35)
Nasopharynx carcinoma	3 (12)
Adenocarcinoma	2 (8)
Acinic cell carcinoma	1 (4)
Hurthle cell carcinoma	1 (4)
Prior RT dose, Gy	
Median (range)	60 (45–72)
GTV, cm ³	
Median GKS (range)	4.2 (1.9–12.4)
Median GKE (range)	9.7 (4.9–23.7)
GKS (n = 22)	
Dose (range)	17 (15–20)
BED ₆ (Gy)	58.7
BED ₁₀ (Gy)	41.6
% normalization (range)	50 (43–55)
GKE (n = 4)	
3-fraction dose (range)	24 (21–27)
BED ₆ (Gy)	56
BED ₁₀ (Gy)	43.2
% normalization (range)	46 (45–50)
Facial pain distribution, no. (%)	
Rt side	14 (54)
V1	1 (4)
V2	3 (12)
V3	4 (15)
Multiple	18 (69)
Numbness	16 (62)
Recurrence site	
Cavernous sinus	5
Cavernous sinus/V1	1
Cavernous sinus/V2	3
Cavernous sinus/V2–3	2
Cavernous sinus/brainstem	3
Meckel's cave	1

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TABLE 1. Patient and treatment characteristics

Variable	Value
Recurrence site (<i>continued</i>)	
Meckel's cave/V3	1
Meckel's cave/V2–3	4
Foramen ovale	1
Foramen ovale/V3	2
Petrous apex	3

BED₆ = biologic effective dose for an assumed alpha/beta ratio of 6; BED₁₀ = biologic effective dose for an assumed alpha/beta ratio of 10; GTV = gross tumor volume; RT = radiotherapy.

3–6 months ($p < 0.001$) and 1.19 at 6–12 months ($p < 0.01$) from 4.65 months pretreatment. Mean NRS scores at more than 1 year of follow-up were available for 8 patients and showed an improvement of 3.9 points, from 4.65 to 0.75 ($p < 0.01$). Similarly, mean MDASI-HN pain scores significantly improved from a pretreatment score of 5.02 to 2.02 at 3–6 months ($p < 0.01$) and trended toward improvement to 1.22 at 6–12 months ($p < 0.15$). On correlative analyses, there was no association between improvement in pain and histology, treatment dose, treatment volume, or GKRS versus GKE.

In the 7 patients with disease progression, 3 patients did not report any improvement and 4 developed recurrence of facial pain after initial improvement. Of the 3 patients with no improvement in pain, 2 had disease progression at the first follow-up evaluation (1.8 and 2.2 months) and the third showed progression at 4.6 months after an initial

TABLE 2. Patient treatment response

Variable	Value
Patients with LR/progression, no. (%)	
Yes	7 (27)
No	19 (73)
Time to LR/progression (mos)	
Median (range)	2.8 (1.2–6.8)
LR/progression treatment modality, no.	
GKS	7
GKE	0
Deaths attributed to LR/progression, no.	
Yes	7
No	0
Patient tumor response, no. (%)	
Yes	19 (73)
CR/Near CR	4 (15)
PR	9 (35)
Stable disease	6 (23)
No	7 (27)
Time to radiographic treatment response (mos)	
Median (range)	6.3 (4.4–8.1)

CR = complete response; LR = local recurrence; PR = partial response.

TABLE 3. Patient response to pain relief and analgesic use in responders and nonresponders to treatment

Variables	Nonresponders			Responders						
	Pre-GKRS (n = 7)	Post-GKRS 3–6 Mos (n = 7)	p Value	Pre-GKRS (n = 19)	Post-GKRS 3–6 Mos (n = 19)	p Value	Post-GKRS 6–12 Mos (n = 16)	p Value	Post-GKRS >1 Yr (n = 8)	p Value
Mean NRS score $\pm$ SD	4.45 $\pm$ 3.09	3.40 $\pm$ 2.06	NS	4.65 $\pm$ 3.45	1.47 $\pm$ 2.11	<0.001	1.19 $\pm$ 1.87	<0.01	0.75 $\pm$ 2.12	<0.01
Mean MDASI-HN pain score $\pm$ SD	4.7 $\pm$ 2.29 (n = 4)	3.75 $\pm$ 1.92 (n = 4)	NS	5.02 $\pm$ 1.68 (n = 13)	2.02 $\pm$ 1.54 (n = 13)	<0.01	1.22 $\pm$ 1.39 (n = 9)	NS	NA	NS
Excellent response (pain free & no analgesics)	0	0	0	0	10/19		9/16		6/8	
Good response (pain free on analgesics)	0	0	0	0	5/19		4/16		2/8	
BNI score										
I	0	0	0	0	8/19		7/16		5/6	
II	0				2/19		2/16		1/6	
IIIa	0				7/19		6/16		NA	
IIIb	0				1/19		1/16		NA	
IV & V	7/7	7/7		19/19	1/19		NA		NA	
PRN analgesics (frequency of daily use $\pm$ SD)	0.88 $\pm$ 0.28	0.31 $\pm$ 0.61	0.10	0.49 $\pm$ 0.55	1.33 $\pm$ 0.90	0.08	2.32 $\pm$ 2.16	0.15	NA	
Baseline opioid use (FED $\pm$ SD, mcg/hr)	36.4 $\pm$ 45.4	21.1 $\pm$ 42.1	NS	62.4 $\pm$ 102.1	27.9 $\pm$ 45.5	<0.001	24.6 $\pm$ 58.2	<0.01	0	
PRN opioid use (daily OMED $\pm$ SD, mg/day)	79.2 $\pm$ 157	28.8 $\pm$ 33.0	0.21	43.9 $\pm$ 77.5	10.9 $\pm$ 20.8	0.02	11.5 $\pm$ 24.5	NS	0	

NA = not applicable; NS = not significant.

GKRS includes patients treated with GKS and GKE.

follow-up evaluation at 2 months showing stable disease. Of the 4 patients with facial pain recurrence, all demonstrated local disease progression and/or recurrence on imaging. The median duration between symptom recurrence and radiographic confirmation of recurrence/progression was 1.2 months (range 0.4–2.8 months)

Opioid and Nonopioid Analgesic Use

The patients were evaluated for narcotics use. Among the 19 patients without disease progression or recurrence, the median follow-up duration was 12.2 months (range 3.5–87.4 months). A reduction in both baseline opioid (mean FED change of 39.2 mcg/hr) and PRN opioid (mean OMED change of 35.8 mg/day) use was observed at 3–6 months ($p < 0.05$ for both). Similarly, at 6–12 months follow-up, both baseline and PRN opioid use were significantly decreased (mean change in FED of 42.5 mcg/hr and OMED of 35.2 mg/day; $p < 0.05$). There was a trend for decreased frequency of PRN nonopioid analgesic use from a pretreatment mean score of 0.49 to 1.33 at 3–6 months ($p = 0.08$) and 2.32 at 6–12 months ($p = 0.15$). Three patients were on neuromodulator therapy (all gabapentin) prior to radiosurgery for their facial pain, and the dose and frequency of gabapentin did not change after radiosurgery. Among the 7 patients with local disease progression, the pretreatment baseline opioid use was 36.4 $\pm$ 45.4 mcg/hr and PRN opioid use was 79.2 $\pm$ 157 mg/day. At 3–6 months, baseline opioid use was 21.1 $\pm$ 42.1 mcg/hr ($p = 0.57$ vs pretreatment) and PRN opioid use was 28.8 $\pm$ 33 mg/day ($p = 0.22$ vs pretreatment).

Discussion

A limited number of studies have evaluated the role of GKRS for local control either as a boost to fractionated external beam therapy or as salvage treatment in the recurrent setting. The few patients with malignant tumors treated with GKRS for symptom palliation are analyzed in aggregate among those with benign tumors where malignant tumors represent < 5% of the study population. In this paper we report the first series of GKRS for tumor control, symptom palliation, and opioid use/dependency in those with perineural disease skull base recurrence who have intractable facial pain because of tumor. At the first follow-up evaluation, any pain relief occurred in 18 (95%) of the 19 patients without local progression or recurrence. Complete pain relief was reported in 15 (79%) of 19 patients between 3 and 6 months, and in 13 (81%) of 16 patients between 6 and 12 months; there was a concomitant decrease in baseline and PRN opioid dependency following GKRS at these time points ($p < 0.05$).

The role of 3D conformal radiation therapy or intensity-modulated radiation therapy re-irradiation for symptom palliation is associated with response rates in the range of 40%–65%.^{10,19,20} Surgery, through cytoreduction and direct decompression of the trigeminal nerve, is considered the most effective means to achieve pain control. Rates of complete initial pain relief in surgical series were more than 80% in those who do not respond to medical management.² However, surgical palliation is limited by the required surgical expertise, difficulty in achieving adequate

resection of skull base tumors, and the possible surgical morbidity risk, which represent limitations of this approach.

GKRS is a less-invasive alternative for palliation of TN secondary to benign skull base tumors. In general, GKRS offers effective symptom relief, albeit outcomes appear less favorable compared with surgery. The largest series using GKRS for treatment of tumor-associated trigeminal pain was reported by Regis et al.²⁶ Fifty-three patients with skull base tumors, both benign ($n = 51$) and malignant ($n = 2$, cerebral metastasis), were evaluated. At a median follow-up of 55 months, 78% of patients achieved complete pain relief and 14% had partial pain relief. Recurrence of pain occurred in 6 (13.3%) of 45 evaluable patients. Similarly, Tanaka et al.³³ evaluated 31 patients treated with SRS for trigeminal pain secondary to skull base tumors (all benign). They showed a complete pain response in 58% of patients, with 23% being pain free and off medications. However, only a quarter of the patients retained durable pain control at last follow-up.

In both the Regis et al. and Tanaka et al. studies, radiosurgery was directed at the tumor. A recent study done at the University of California, Los Angeles, evaluated a provocative question, i.e., that perhaps the optimal strategy to achieve pain relief in patients with tumor-associated trigeminal pain is to target the trigeminal nerve (as in the treatment of idiopathic TN) instead of the primary lesion.⁹ In this study, 12 patients were evaluated. The majority (83%) had benign tumors (meningioma $n = 8$, vestibular schwannoma $n = 1$, hemangiopericytoma $n = 1$), with 2 patients having squamous cell carcinoma. Ten of the 12 patients initially received radiation therapy targeting the tumor, with 60% reporting partial pain relief after a mean duration of 6 months. All 12 patients eventually received SRS targeting the trigeminal nerve for facial pain, with 10 patients (83%) experiencing “good initial” pain relief and 6 (50%) reporting complete pain relief. Recurrence of pain occurred in 6 (50%) with a mean duration of pain relief of 41 months after radiosurgery. The authors concluded that targeting the trigeminal nerve provided more durable pain relief comparable to surgical interventions.

In the current study, all patients had malignant tumors and the treatment target was the tumor. The pain relief observed correlated with a significant reduction in both NRS score (from 4.60 at baseline to 1.47 at 3–6 months and 1.19 at 6–12 months) and MDASI-HN pain scores (from 5.02 at baseline to 2.02 at 3–6 months and 1.22 at 6–12 months). Notably, in the 8 evaluable patients without evidence of local progression at 1 year posttreatment, 100% were pain free, indicating a durable response.

Although opioid use is necessary to alleviate tumor-associated pain conditions, their chronic use is associated with an increase in risk of mortality and morbidity.^{1,15} As such, providers often seek assistance from pain specialists for those who have high daily oral morphine equivalent requirements. To date, a thorough and systematic evaluation of opioid dependency after GKRS has not been reported in the literature. The statistically significant decrease in daily OME in the current cohort suggests that GKRS is an effective alternative to prolonged opioid therapy.

Targeting only the nerve and not tumor may not be as

effective for malignant tumors because of their more aggressive growth pattern. In our study, 7 (27%) of 26 patients had a local recurrence or progression after GKRS. Of these 7 treatment failures, 2 were from in-field tumor progression at first follow-up and 5 were from progression of untreated disease outside the GKRS field after an initial stable finding of the treated portion of tumor. In each of these 5 cases, prior treatment effects made it challenging to identify the full extent of disease and/or proximity to a critical neurooptic structure precluded delivery of GKRS to the entire volume of disease. In retrospect, these areas of uncertainty, which were near the brainstem or distally along the cranial nerve V3 in the masticator space, eventually progressed and likely harbored tumor. Although the use of GKE allowed for treatment of more extensive tumors by delivering a higher total dose in 3 fractions, the mouthpiece was difficult to tolerate and required patients with calm personalities, good dentition, and minimal gag reflex.

Colleagues from the Mayo Clinic have evaluated the role of GKRS for local control of gross residual disease in the recurrent setting or as a boost to fractionated external beam therapy. Owen et al. evaluated 184 patients with primary and recurrent head and neck malignancies in which SRS (delivered as a single fraction) was used as a component of their treatment.^{22,23} Forty-six percent of patients had involvement of the cavernous sinus or skull base. Thirty-one percent of patients received radiosurgery as a boost to chemoradiation and 61% received SRS as salvage therapy for recurrent disease. The local control rate at 12 months was 82%. The median progression-free survival was 16 months for those treated with curative intent, whereas it was 8 months for those treated with palliative intent. Late effects occurred in 59 patients, with the most common being temporal lobe necrosis (15 patients). Similarly, in the study by Tanaka et al., radiosurgery was directed at the benign tumor with excellent 5-year local control rates of 95%, although additional therapies were needed to achieve durable symptom palliation.

In our study population, in which the primary goal is tumor control with a secondary goal of symptom palliation, acute worsening of facial pain was a potential concern, particularly because these patients had received prior radiation and subsequently underwent radiation treatment again with ablative doses to perineural disease in the skull base. We found that the use of intravenous steroids immediately after GKRS followed by a short-course oral steroid taper mitigated these acute events to 1 patient, which occurred early in our experience. Interestingly, we found that in all instances of local disease progression or recurrence following GKRS, worsening of clinical symptoms preceded imaging findings of tumor progression, thus serving as a clinical pretest predictor of tumor recurrence. These results highlight the challenge of determining the optimal GKRS treatment volume and overlapping role of GKRS for both symptom palliation and local control in those with recurrent skull base malignancies.

This study has inherent limitations as a retrospective assessment of a small patient cohort treated at a tertiary center; therefore results may not be generalizable. The outcomes and toxicity associated with treatment were

determined based on a review of medical records, which rely on accurate clinical documentation and may underestimate events or side effects. While some patients were lost to clinical follow-up, the majority of patients did obtain timely and complete clinical evaluation posttreatment. Although we did not observe late treatment effects, the median follow-up for this group was less than 12 months. Opioid requirement prior to GKRS may not take into account other indications for narcotic use. Additionally, the use of anticonvulsants or antidepressants for neuropathic pain were not measured. This study did not evaluate objective measures of patient function or other “functional” patient-reported outcome items to assess the impact of pain response on quality of life measures such as the ability to return to work and complete activities of daily living after GKRS. Given the disease rarity and novel treatment approach, our series is unique. It represents a cohort with locally advanced recurrent disease of the skull base treated in a uniform manner using modern radiotherapy techniques not previously described.

Conclusions

GKRS provides good local control for patients with recurrent skull base malignancies with minimal re-irradiation toxicity. For those with malignant tumors resulting in trigeminal pain, GKRS offers effective symptom palliation and reduces the narcotic requirement. In the absence of tumor recurrence, the majority of patients expressed durable pain palliation at 1 year after treatment. Conversely, symptomatic progression after GKRS may be a harbinger of disease recurrence and should prompt clinical workup. The use of GKRS to treat patients with complex neuropathic trigeminal pain from malignant tumor recurrence should continue to be investigated.

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Disclosures

Dr. Frank reports being a consultant to Varian.

Author Contributions

Conception and design: Phan, DeMonte. Acquisition of data: Phan, Pollard, Yang, Luo, Wang, Raza. Analysis and interpretation of data: all authors. Drafting the article: Phan, Pollard, Brown, Gidley, DeMonte. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Phan. Statistical analysis: Phan, DeMonte. Study supervision: Phan, DeMonte.

Supplemental Information

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Correspondence

Jack Phan: The University of Texas MD Anderson Cancer Center, Houston, TX. jphan@mdanderson.org.