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Radiosurgery of Glomus Tumors of Temporal Bone: a Meta-analysis

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Objective: 1) Perform a meta-analysis of the available data on the outcomes of stereotactic radiosurgery (SRS) for the treatment of temporal bone glomus tumors (GT), and 2) evaluate the collective outcomes of SRS treatment with respect to tumor control.

Data Sources: A thorough literature search of the published English-language literature from 2011 to 2016 was performed in PubMed, Ovid, and Cochrane databases using the keywords (“Gamma Knife” or “CyberKnife” or “linear accelerator” or “radiosurgery”) and (“glomus jugulare” or “jugular paraganglioma” or “glomus tympanicum”).

Study Selection: Studies reporting outcomes of SRS for temporal bone GT were included.

Data Extraction: Of 45 articles found, 15 studies met our inclusion and exclusion criteria and were selected for qualitative and quantitative analyses totaling 511 patients.

Data Synthesis: Average margin dose, modality, isodose line, volume decrease, follow-up duration, and tumor control rate data were extracted and analyzed.

Conclusion: Gamma Knife was the most commonly implemented radiosurgery modality and was used in eight studies. The mean marginal dose varied between 13.2 and 20 Gy. The pooled tumor control rate was 95.4% (95% CI: 93.6–97.2%) over a median follow-up duration ranging between 27.4 and 148 months. Clinical data on outcomes of SRS for the treatment of GTs are sparse and primarily limited to single institutional analyses, with considerable variation in tumor volume and follow-up duration. This meta-analysis provides an in-depth analysis of the available data in the literature and reviews the reported outcomes. Future studies on SRS for GT should include data on tumor growth before radiation as well as follow-up periods sufficiently long to identify true tumor control. **Key Words:** CyberKnife—Gamma Knife—Glomus tumors—Glomus tympanicum—Paraganglioma—Radiation therapy—Radiosurgery—Stereotactic surgery—Temporal bone.

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Glomus tumors (GT) of the temporal bone were first described in 1945 by Rosenwasser (1). These relatively rare tumors are primarily treated with microsurgery, stereotactic radiosurgery (SRS), or combined therapy (2,3). For glomus tympanicum tumors, surgery is often the preferred management method as these tumors are smaller and surgical excision generally offers complete relief. For glomus jugulare tumors, the best treatment approach is decided on the basis of several factors

including the location of the tumor and associated symptoms. Surgical excision is often favored if there is brainstem compression or intracranial hypertension. In other cases, similar control rates between SRS and surgery with or without preoperative embolization and/or adjuvant radiation have been reported (4).

There has been an increasing interest in SRS for GTs in recent decades given similar control rates and potentially lower complication rates when compared with surgical excision (5). Various radiation modalities have been used including Gamma Knife (GK), CyberKnife (CK), and linear accelerator (LINAC). Most studies investigating the outcomes of SRS have been limited to single institutions with relatively small sample sizes and variable follow-up duration. A meta-analysis conducted in 2011 (6) reported a high tumor control rate with SRS; however, limited radiation parameters were reported and it included studies published up to 2010. In the current study, we aimed to 1) perform a meta-analysis of recent published studies on the outcomes of SRS for the GT treatment since 2011, and 2) evaluate the collective tumor control rate of SRS.

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FIG. 1. Study inclusion flowchart.

METHODS

The PRISMA Guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed for designing and conduction of the study (7). This study was exempt from Institutional Review Board evaluation due to noninvolvement of human subjects and conduction of a literature review only. PubMed, Ovid, and Cochrane databases were queried using the following keywords: (“Gamma Knife” or “CyberKnife” or “linear accelerator” or “radiosurgery”) and (“glomus

jugulare” or “jugular paraganglioma” or “glomus tympanicum”). Articles published during 2011 to 2017 and reporting GT outcomes following SRS were investigated. Figure 1 illustrates the PRISMA flowchart of the study. Review articles and non-English-language studies without translation were excluded. The full text of the remaining studies was independently reviewed for relevance by two of the authors. Studies were included if they reported outcomes of treating GTs of the temporal bone with radiosurgery. Studies in which data for temporal bone GTs were not separated from other head and neck paragangliomas were excluded. If disagreement occurred for inclusion, the senior author acted as the final arbitrator (Fig. 2).

For each study, period of data collection, patient demographics, tumor type and size, radiation technique/modality, prevalence of previous treatments, radiation dose, volume decrease percentage, follow up duration, and tumor control rate were extracted. The tumor type in some studies was reported as either glomus jugulare or tympanicum, whereas in others it was based on the Fisch classification (8). Statistical analyses were performed using OpenMeta[Analyst] (Brown University, Providence, RI) using the random effect model. The collective mean and 95% confidence intervals (CI) were calculated for the collective tumor control rate.

RESULTS

Fifteen studies met the inclusion/exclusion criteria (Table 1) and were analyzed (9–23). These studies contained 511 patients studied during 1988 to 2015. The mean sample size ranged from 11 to 134 patients. Females comprised the majority of the patients in all studies (range 53–93%). Fisch classification of the tumors was only reported in six studies and the vast majority of the patients in these studies had a tumor Fisch class of C or higher. The mean tumor size varied between 3.6 and 33 mL. A minority of patients in almost all studies had a previous treatment including surgical resection, embolization, or conventional radiation.

Studies	Estimate (95% C.I.)	Ev/Trt
Lee 2011	0.967 (0.876, 1.000)	14/14
Kunzel 2012	0.955 (0.831, 1.000)	10/10
Sheehan 2012	0.927 (0.881, 0.973)	114/123
Hurmuz 2013	0.967 (0.876, 1.000)	14/14
Gandia-Gonzalez 2014	0.948 (0.891, 1.000)	55/58
Liscak 2014	0.977 (0.933, 1.000)	43/44
Sager 2014	0.974 (0.902, 1.000)	18/18
Wong 2014	0.933 (0.807, 1.000)	14/15
El Majdoub 2015	0.982 (0.933, 1.000)	27/27
Scheick 2015	0.818 (0.590, 1.000)	9/11
Dobberpuh 2016	0.962 (0.857, 1.000)	12/12
Hafez 2016	0.955 (0.868, 1.000)	21/22
Schuster 2016	0.929 (0.794, 1.000)	13/14
Ibrahim 2016	0.947 (0.896, 0.998)	71/75
Winford 2017	0.818 (0.687, 0.950)	27/33
Overall ($I^2=0\%$, $P=0.766$)	0.954 (0.936, 0.972)	462/490

FIG. 2. Forest plot pooled tumor control.

TABLE 1. Details of the published studies on outcomes of stereotactic radiosurgery for glomus tumors

Citation	Institution, Country	Years	Sample Size (Female %)	Mean Age (Range, y)	Tumor Type	Mean Tumor Size (Range, ml)	Previous Treatments	Misc
Lee 2011 (10)	Taipei Veterans General Hospital, Taiwan	1993–2009	14 (86%)	42.3 ^a (22–68)	11 GT 3 GJ	9.5 ^a (6.5–22.1)	2 Partial resections 1 Embolization 2 Conventional radiosurgery	43% vol reduction in 10 w/ > 2 y f/u 11 fractionated SRT 1 Gamma Knife
Kunzel 2012 (11)	Erlangen–Nuremberg University Hospital, Germany	2000–2010	12 (83%)	70 (35–85)	1 Fisch A 3 Fisch B 7 Fisch C 1 Fisch D2	NA	Some had preop embolization	
Sheehan 2012 (12)	Multiple sites, US	1988–2010	134 (63%)	58.7 (18–88)	3 Fisch A 9 Fisch B 69 Fisch C 47 Fisch D 6 Missing	7.8 (0.6–58.6)	38.1% Partial resection 5.2% Radiation	11 lost to f/u Outcome N 123
Hurmuz 2013 (13)	Hacettepe University, Turkey	2007–2010	14 (93%)	68 ^a (31–76)	14 GJ	15.8 (2–64)	1 previous resection	–
Gandía-González 2014 (14)	International Ruber Hospital of Madrid; Spain	1995–2012	58 (69%)	52.4 (19–82)	Unspecified	12 (0.3–62.2)	18 previous resections 10 embolization 4 radiation	
Liscak 2014 (15)	Na Homolce Hospital Prague, Czech Republic	1992–2003	44 (72%)	56 (21–79)	40 GJ 6 GT	3.6 (0.2–24.3)	21 previous resections 8 embolization 2 radiotherapy	2 lost to f/u 15 w/ intracranial tumor spread 18 had adequate f/u
Sager 2014 (16)	Gulhane Military Medical Academy, Turkey	1998–2013	21 (71%)	55 ^a (24–77)	Unspecified	17 ^b (9–31)	5 previous surgery	
Wong 2014 (17)	Royal Adelaide Hospital, Australia	1996–2012	15 (80%)	62 (14–79)	Unspecified	33 ^b (12–110)	4 previous surgery	
El Majdoub 2015 (18)	University Hospital of Cologne, Germany	1991–2011	27 (81%)	57.2 (28–79)	All Fisch D1 or D2	12.2 (2.8–51)	12 previous surgery	
Scheick 2015 (19)	University of Florida, US	1997–2012	11 (81%)	50 ^a (30–88)	11 GJ 1 GT	NA	2 previous surgery	
Dobberpuhl 2016 (20)	University of Kentucky Medical Center, US	1999–2013	12 (77%)	62.8 (31–77)	11 Fisch C 1 Fisch D1	8.4 (2.3–23.2)	NA	
Hafez 2016 (21)	International Medical Center Cairo, Egypt	2005–2011	22 (86%)	46.8 (22–72)	All GJ	7.2 (2.8–19.4)	3 embolization 2 previous surgery 2 radiation	
Schuster 2016 (22)	Vanderbilt University Medical Center, US	1998–2014	14 (71%)	55 ^a (35–79)	All GJ	7.6 (2.2–30.6)	3 previous surgery	
Ibrahim 2016 (23)	National Centre for Stereotactic Radiosurgery, UK	1994–2010	75 (53%)	55 ^a (21–84)	2 Fisch A 17 Fisch B 30 Fisch C 20 Fisch D1 7 Fisch D2	9.1 (0.2–53.9)	24 previous surgery 3 embolization 1 radiotherapy	12 w/ familial paraganglioma
Winford 2017 (9)	Wake Forest University Baptist Medical Center, US	2000–2015	38 (82%)	62.7 (15–88)	5 Fisch B 21 Fisch C 12 Fisch D	5.8	4 previous surgery 1 radiation	1 catecholamine secreting tumor 33 only had radiographic f/u

^aMedian is reported instead of mean.^bMaximal diameter in mm was reported instead of volume.

TABLE 2. Details of the published studies on outcomes of stereotactic radiosurgery for glomus tumors

Citation	Modality	Mean Prescribed Dose (Range, Gy)	Mean Marginal Dose (Range, Gy)	Mean # of Isodose Centers (Range)	Isodose Level (Range, %)	Volume Decrease (Range, %)	Follow-up (Range mo)	Tumor Control Rate (%)	Cranial Nerve Preservation Rate (%)	Complications
Lee 2011 (10)	GK	18.3 (16.7–20.3)	13.7 (12.5–15.0)	16.1 (10–28)	58 (55–60)	34 ^a (3–79)	40.3 ^a (13–143)	14/14 (100)	13/14 (92.7)	1 facial palsy 1 hearing impairment
Kunzel 2012 (11)	SRT GK	SRT 50 (32–54) GK 18	NA	NA	NA	NA	37.5 (4–85)	10/10 [†] (100)	4/6 (67)	1 facial palsy 1 hearing impairment
Sheehan 2012 (12)	GK	30.9 (14–50)	14.8 (10–18)	9.2 (1–20)	50 (30–60)	NA	50.5 ^a (5–220)	114/123 (93)	NA	1 glossohyaryngeal palsy
Hurmuz 2013 (13)	CK	25 (18–30)	NA	NA	80 (70–88)	NA	39 (7–60)	14/14 (100)	NA	None
Gandia-González 2014 (14)	GK	25.2 (18–55)	13.6 (11–15)	10.8 (2–29)	55.3 (40–65)	40.1 (5–95)	86.4	55/58 (95)	NA	4 hearing impairment 1 dysphagia
Liscak 2014 (15)	GK	40 ^a (30–60)	20 ^a (10–30)	NA	NA	50 ^a (10–100)	118 ^a (12–217)	43/44 (98)	NA	–
Sager 2014 (16)	LINAC	15 ^a (10–20)	NA	NA	NA (85–100)	NA	49 ^a (3–98)	18/18 (100)	NA	–
Wong 2014 (17)	2 (SRS) 13 (EB)	NA	13 and 18 (SRS) 45–50.4 (EB)	NA	NA	NA	48 (1–364)	14/15 (93)	NA	–
El Majdoub 2015 (18)	LINAC	20.3 (15–33.9)	14.8	NA	74.3 (44–92)	48.7 (33.3 – 91)	148 (64–266)	27/27 (100)	NA	–
Scheick 2015 (19)	SRS	15 ^a (12.5–15)	NA	NA	NA	NA	64 ^a (32–199)	9/11 (81)	NA	–
Dobberpuhl 2016 (20)	GK	31.2 (25–36)	15.5 (12–18)	12.1 (2–20)	50.8 (50.60)	37 (0.8–77)	27.6 (13–96)	12/12 (100)	NA	–
Hafez 2016 (21)	GK	41 (34–45)	14.7 (12–16)	NA	37.7 (35–50)	NA	56 ^a (36–108)	21/22 (95)	NA	–
Schuster 2016 (22)	LINAC	Single fraction 15–18 Fractionated 26.2 (21–45)	NA	NA	76.5 (39–90)	NA	31.7 (18.6–56.1)	13/14 (93)	NA	–
Ibrahim 2016 (23)	GK	37.3 (23.2–50)	18.3 (12–25)	12.1 (2–44)	49.6 (40–56)	5.5	51.5 ^a (12–230)	71/75 (93)	NA	–
Winford 2017 (9)	GK	26.3 (15.6–30.0)	13.2 (11–15)	17 (1–46)	NA	NA	39.1 (5.5–141.0)	27/33 (82)	NA	–

^aMedian is reported instead of mean.

SRT indicates stereotactic radiation therapy; EB, external beam; CK, Cyber Knife; SRS, stereotactic radiosurgery; GK, Gamma Knife; LINAC, linear accelerator; NA, not available.

Gamma Knife was the most common radiosurgery modality and was used in eight studies (Table 2). The mean marginal dose varied between 13.2 and 20 Gy. The pooled tumor control rate was 95.4% (95% CI: 93.6–97.2%; $p < 0.001$) over a median follow-up duration ranging between 27.4 and 148 months. The Forest plot for the pooled analysis is presented in Figure 1. In all the studies, tumor control was defined as stable or decreased tumor size after radiosurgery except for the study by Winford et al. (9) where a tumor growth less than 10% after radiosurgery was also considered tumor control.

Two subanalyses were performed on the studies with longer follow-ups. The first one was on the eight studies with at least a minimum follow-up of 12 months as observed in Table 1. The pooled tumor control rate in these studies was 96.5% (95% CI: 94.1–98.9%). The second one was on the three studies with at least 32 months of follow-up, as observed in Table 1. The pooled tumor control rate in these studies was 96.9% (95% CI: 92.6–100.0%).

DISCUSSION

GT patients treated with SRS have a pooled tumor control rate of 95.4%. A subanalysis performed on the eight studies with a 12-month or greater follow-up period demonstrated a 96.5% pooled tumor control rate. SRS and surgery are comparable treatment options for GTs and are both safe and efficacious. The ideal treatment approach should be tailored to each tumor's unique characteristics and patient's associated comorbidities. Surgery, wherever possible, may offer instant and oftentimes complete resection of the tumor, despite higher morbidity rates (24). On the other hand, SRS has a lower morbidity rate, although the incidence of long-term recurrence of the tumor (i.e., following 10–20 yrs) remains unknown (24). Therefore, the optimal therapeutic intervention for GTs remains uncertain, with microsurgical intervention resulting in higher morbidity rates and lower tumor control rates than SRS. The larger tumors will oftentimes require microsurgical debulking with adjunctive SRS (25). Left untreated, GTs rarely metastasize and are relatively benign and slow growing with a low associated mortality rate (26). Several studies have demonstrated that cervical paragangliomas have a slow rate of growth, with approximately 60% of tumors not exhibiting growth over follow-up periods similar to those reported in the present study (27,28). Another study looking at GTs found that 58% of the tumors did not demonstrate growth over the study period (29). As such, the patients need to be counseled accordingly and further studies will be warranted to compare SRS to the wait-and-scan strategy. Nevertheless, the mass effect from uncontrolled GT growth can compromise the surrounding brain or cranial nerves and may necessitate surgical or SRS intervention. Even though SRS offers enhanced maneuverability of the radiation dose in difficult-to-reach areas, there is a tradeoff between higher radiation doses and toxicity to the surrounding tissues.

This tradeoff must be carefully considered in the presurgical planning.

In this meta-analysis, we report a pooled tumor control rate of 95.4%, which is similar to the previously reported 95% control rate from a previous meta-analysis containing 869 patients (6) and (97)% control rate from a meta-analysis containing 335 patients (5). These tumor control rates are higher than the 85% tumor control rate reported for gross-total resection and 71% tumor control rate for subtotal resection with SRS, despite a greater fraction of patients undergoing SRS having Fisch Class D tumors (6). SRS can result in better tumor control rates than microsurgical resection, and is ideal for smaller tumors (30). However, it must be noted that the pooled control rate in this meta-analysis is limited due to the variable lengths of follow-up in the included studies. The high tumor control rates reported for SRS are likely an overestimate of the true tumor control rate, as some patients had previously undergone surgical resection as well as preoperative embolization. This signifies the need for a multidisciplinary approach to GT treatment and the need to tailor treatments to the unique needs of each patient based on specific tumor characteristics. In addition, tumors that undergo surgical resection may be more complicated and certain areas may be harder to resect yielding a lower control rate.

Although the follow-up period in some of the studies was limited, two subanalyses performed on studies with longer than 12 or 32-month follow-up periods demonstrated a 96.5% and 96.9%, respectively, pooled tumor control rate that did not statistically differ from the 95.4% pooled tumor control rate across all the studies. This indicates that although some of the studies had relatively limited follow-up data, the primary outcome we queried did not significantly differ between the studies with follow-up periods shorter or longer than 12 or 32 months.

Although great care was taken to ensure the validity of our results and ensure that all studies published after the 2011 meta-analysis by Ivan et al. were included, there remain a number of limitations. Notably, all the SRS modalities were included in the meta-analysis, and information such as tumor size and treatment-specific data was not included in all the studies examined. All included studies were uncontrolled case-series, with a heterogeneous patient populations, tumor management, tumor type/size, radiation modality, and tumor control definition. Other limitations include a lack of consistent inclusion criteria among the included studies and insufficient information regarding attrition rate of patients, which was reported in only four studies. In addition, tumor control was only reported in 6 of the 15 studies. Furthermore, stage-specific stratification of patients and treatments was not reported in these studies. This review is also limited by the quality and precision of the data reported in the studies examined. Lastly, longer follow-up periods would be required to draw meaningful conclusions with respect to SRS effectiveness. Ultimately, these limitations may affect the reliability of the reported results, which likely overestimate the true

tumor control rate. Nonetheless, this meta-analysis and literature review provides an in-depth analysis of the contemporary literature on the SRS of GTs and estimates a pooled tumor control rate for SRS in general.

CONCLUSION

This meta-analysis and literature review provides an in-depth analysis of contemporary literature on SRS treatment of GTs and estimates the corresponding pooled tumor control rate. We report a pooled tumor control rate of 95.4%, which is comparable to the previously reported tumor control rates. A subanalysis performed on the 8 studies with a 12-month or greater follow-up period demonstrated a 96.5% pooled tumor control rate that did not statistically differ from the 95.4% pooled tumor control rate across all the studies.

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