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# Image-guided robotic radiosurgery for glomus jugulare tumors—Multicenter experience and review of the literature

**Felix Ehret MD[1] | Markus Kufeld MD[1] | Christoph Fürweger PhD[1,2] | Alfred Haidenberger MD[1] | Christian Schichor MD, MHBA[3] | Ralph Lehrke MD[4] | Susanne Fichte MD[5] | Carolin Senger MD[6] | Martin Bleif MD[7] | Daniel Rueß MD[2] | Maximilian Ruge MD[2] | Jörg-Christian Tonn MD[3] | Alexander Muacevic MD[1] | John-Martin Hempel MD[8]**

[1]European Cyberknife Center, Munich, Germany

[2]Department of Stereotaxy and Functional Neurosurgery, Center for Neurosurgery, University Hospital Cologne, Cologne, Germany

[3]Department of Neurosurgery, Ludwig-Maximilians-University Munich, Campus Grosshadern, Munich, Germany

[4]German CyberKnife Center, Soest, Germany

[5]CyberKnife Center Mitteldeutschland, Erfurt, Germany

[6]Charité CyberKnife Center, Charité – Universitätsmedizin Berlin, Berlin, Germany

[7]Radiochirurgicum/CyberKnife Südwest, Göppingen, Germany

[8]Department of Otorhinolaryngology and Head and Neck Surgery, Ludwig-Maximilians-University Munich, Campus Grosshadern, Munich, Germany

**Correspondence**
Felix Ehret, European Cyberknife Center, Max-Lebsche-Platz 31, Munich 81377, Germany.
Email: felix.ehret@campus.lmu.de

**Funding information**
Munich Medical Research School, Ludwig-Maximilians-University Munich

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## Abstract

**Background:** Glomus jugulare tumors (GJTs) are challenging to treat due to their vascularization and location. This analysis evaluates the effectiveness and safety of image-guided robotic radiosurgery (RRS) for GJTs in a multicenter study and reviews the existing radiosurgical literature.

**Methods:** We analyzed outcome data from 101 patients to evaluate local control (LC), changes in pretreatment deficits, and toxicity. Moreover, radiosurgical studies for GJTs have been reviewed.

**Results:** After a median follow-up of 35 months, the overall LC was 99%. Eighty-eight patients were treated with a single dose, 13 received up to 5 fractions. The median tumor volume was 5.6 cc; the median treatment dose for single-session treatments is 16 Gy, and for multisession treatments is 21 Gy. Fifty-six percentage of patients experienced symptom improvement or recovered entirely.

**Conclusions:** RRS is an effective primary and secondary treatment option for GJTs. The available literature suggests that radiosurgery is a treatment option for most GJTs.

**KEYWORDS**

CyberKnife, glomus jugulare, paraganglioma, radiosurgery, review

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## 1 | INTRODUCTION

With an estimated incidence of around one per 1.3 million people, glomus jugulare tumors (GJTs) are rare, well-vascularized neuroendocrine tumors arising from the adventitial chemoreceptor tissue of the jugular bulb.[1] They are usually of benign histology but are capable of locally infiltrating adjacent tissue like the lower cranial nerves and the temporal bone. In rare cases, GJTs can secret catecholamines and metastasize to lymph nodes and distant organs, which significantly worsens the disease prognosis.[2-4] Due to their location close to the jugular foramen, common symptoms are lower cranial nerve palsies, which lead to dysphagia, dysarthria, pulsatile tinnitus, hearing loss, vertigo, and dysphagia. In hormone-secreting tumors, tachycardia and labile blood pressures are typical findings.[4]

Even with the development of microsurgical techniques, surgical tumor resection remains a challenge for surgeons given the location of the tumor, vascularization and adjacent nerves, and vessels.[5-7] Despite the lack of treatment guidelines, fractionated radiotherapy and single-session radiosurgery (RS) are alternative treatment options, especially for patients not suitable for surgery.[6-8] Due to the rarity of the tumor, many studies investigating RS for the management of GJTs comprised only a small number of patients, additionally included other head and neck paragangliomas, and did not stratify the outcomes for primary and secondary RS. Only a few studies reported long-term follow-up results and only a limited number of studies on the use of image-guided robotic radiosurgery (RRS) are available. To overcome this lack of knowledge and to improve clinical decision making for the primary or postoperative irradiation of GJTs, we conducted a retrospective multicenter study including six centers investigating the use of image-guided RRS for the treatment of GJTs. We also reviewed the radiosurgical literature and compared our results with published data.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

One hundred and one patients with GJTs from six dedicated CyberKnife (CK) centers were treated with RRS between July 2005 and March 2019 and included in this retrospective multicenter study. Patient information including medical history, previous treatments, and follow-up data were stored at each center in the respective electronic health records or patient files. During follow-up appointments, patients were evaluated for clinical symptoms, adverse effects, complications, and treatment response by clinical examination and by magnetic resonance imaging (MRI). Appointments took place 6 and 12 months after treatment delivery. Follow-up was done after 6 months and in 12 months intervals, thereafter if no acute complications occurred. Only patients with at least one completed radiographic and clinical follow-up 6 months after treatment delivery were included in this analysis. GJT diagnosis was either based on histopathological examination (39 patients) or radiographic findings as well as clinical appearance of the patient (62 patients). For radiographic diagnosis, thin-sliced computed tomography (CT), MRI, as well as contrast-enhanced MR angiography (CE-MRA) imaging were used. This study was approved by the respective institutional review board.

### 2.2 | Treatment procedure and outcome

For treatment planning and delivery, thin-sliced, contrast-enhanced CT and MRI scans were used for every patient. Imaging sequences included gadolinium-enhanced T1 and T2 sequences and vessel-focused Time of Flight series. Resulting CT and MRI imaging data were overlaid for treatment planning. Various software tools (MultiPlan, Precision, Accuray Inc., Sunnyvale, California) were used for inverse treatment planning. All patients were treated with single- or multisession (up to 5 fractions) stereotactic RRS in an outpatient setting using a CyberKnife RRS system (Accuray Inc., Sunnyvale, California). During treatment delivery, custom-fitted thermoplastic face masks were used for non-invasive fixation. Tumor volume measurement was done directly with the above-mentioned software assessing the tumor volume on available thin-sliced MRI imaging data before treatment and at last available follow-up. Radiographic assessment of the treatment outcome was defined as follows: Tumor volume reduction (TVR), tumor volume decrease of at least 20%, progressive disease (PD), increase of the overall tumor volume of at least 20%, with local control (LC) defined as no evidence of PD during follow-up imaging. Tumors with volume changes ±20% were considered unchanged. To determine potential prognostic factors, logistic regression models were used following a backward selection approach. For normally distributed and paired data, a paired student's *t* test was conducted. Data were analyzed using STATA 16.0 (StataCorp, College Station, Texas). *P*-values equal to or less than .05 were considered significant.

### 2.3 | Literature review

We used various combinations of keywords including *radiosurgery, stereotactic, cyberknife, gamma knife, LINAC, paraganglioma, chemodectoma*, *glomus jugulare*,

**TABLE 1** Patient characteristics, pretreatment deficits, and pretreatments

| **Patient characteristics** | | | | |
|---|---|---|---|---|
| Total number of patients included | 101 | | | |
| Sex (male/female, %) | 35 (35) | 66 (65) | | |
| | Median | Mean | | Range |
| Age (years) | 56.0 | 57.6 | | 18.8-87.3 |
| Pretreatment Karnofsky performance score (%) | 100 | 91.3 | | 70-100 |
| Follow-up (months) | 35.0 | 44.0 | | 6.0-160.8 |
| Total tumor volume all patients (cc) | 5.6 | 7.5 | | 0.2-42.0 |
| Total tumor volume primary treatment patients (cc) | 6.1 | 8.2 | | 0.4-42.0 |
| Total tumor volume secondary treatment patients (cc) | 3.9 | 6.3 | | 0.2-31.6 |
| Side of the tumor (left/right, %) | 61 (60) | 40 (40) | | — |
| Number of patients treated in single session | 88 | | | |
| Dose (Gy) single session | 16.0 | 15.6 | | 12.0-18.0 |
| Prescription isodose (%) single session | 70 | 70.7 | | 60-80 |
| Number of patients treated in multisession | 13 | | | |
| Number of fractions | 3 | 4 | 5 | |
| Number of patients | 8 | 1 | 4 | |
| Dose (Gy) multisession | 21.0 | 23.1 | | 19.5-30.0 |
| Prescription isodose (%) multisession | 70 | 70 | | 63-77 |
| **Pretreatment deficits** | **All patients** | **Untreated** | | **Pretreated** |
| Number of patients | 101 | 62 | | 39 |
| Patients without deficits | 5 | 1 | | 4 |
| Patients with deficits | 96 | 61 | | 35 |
| Pulsatile tinnitus | 52 | 35 | | 17 |
| Partial hearing loss | 47 | 32 | | 15 |
| Dysphagia | 35 | 19 | | 16 |
| Dysarthria | 33 | 19 | | 14 |
| Vertigo | 30 | 18 | | 12 |
| Total hearing loss | 19 | 8 | | 11 |
| Facial nerve palsy (all degrees) | 15 | 4 | | 11 |
| Feeling of pressure around tumor side | 11 | 9 | | 2 |
| Spinal accessory nerve palsy (all degrees) | 11 | 7 | | 4 |
| Dysesthesia | 10 | 5 | | 5 |
| Pain | 9 | 5 | | 4 |
| Horner syndrome | 4 | 3 | | 1 |
| Cardiovascular complications | 2 | 2 | | 0 |
| Epiphora | 1 | 1 | | 0 |
| **Pretreatments** | | | **Number of patients** | |
| Patients with pretreatments | | | 39 | |
| Single surgery | | | 18 | |
| Single surgery plus tumor embolization | | | 10 | |
| Multiple surgeries | | | 6 | |
| Multiple surgeries plus tumor embolization | | | 3 | |
| Multiple surgeries plus tumor embolization plus fractionated radiotherapy | | | 1 | |

(Continues)

**TABLE 1** (Continued)

| Patient characteristics | |
|---|---|
| Radiosurgery plus single surgery plus tumor embolization | 1 |

*Note:* cc, cubic centimeter, Gy, gray.

and *glomus jugulare tumor* to search published studies for GJTs in the National Library of Medicine database through May 1, 2020. Only studies which reported the primary or secondary radiosurgical treatment of GJTs with up to five fractions were reviewed. Studies which included the treatment of tumor entities other than GJTs were excluded. If an institution or authors had published multiple studies, only the report with the largest sample size was reviewed. Only studies with full-body texts in English were included. To maintain comparability in regard to technological advancements, only studies published after January 1, 2000 were included in this review.

## 3 | RESULTS

### 3.1 | Patient characteristics and treatment parameters

The median age at treatment delivery was 56 years. Most of the treated patients were female (65%) and most of the tumors were located on the left side (60%). The median tumor size was 5.6 cc. Sixty-two out of the 101 (61%) included patients received the treatment as their primary therapy and the majority, 88 out of 101 (87%), were treated in a single session. The median dose for primary and secondary single-session treatments was 16 Gy; the median dose for multisession treatments was 21 Gy in three to five sessions. The median prescription isodose was 70% throughout primary and secondary treatments. The most common pretreatment deficits included pulsatile tinnitus (51%), partial hearing loss (46%), dysphagia (34%), dysarthria (32%), and vertigo (29%). At treatment delivery, five patients (5%) did not show clinical symptoms caused by their GJT. Thirty-nine patients underwent secondary RRS of their tumor. Thirty-eight of them underwent primary surgical resection of their tumor, 10 patients had multiple surgeries up to a maximum of five resections. A summary of the baseline characteristics, treatment parameters, and pretreatment deficits is provided in Table 1.

### 3.2 | Treatment results

The median follow-up time was 35 months (range 6-160). At last follow-up, 23 (24%) patients recovered from their symptoms and 31 (32%) experienced symptom improvement, whereas 35 (34%) reported no significant changes concerning their pretreatment deficits. Five patients (5%) reported a transient worsening of their symptoms before returning to their pretreatment condition at the last available follow-up. Two patients (2%) experienced a persistent worsening caused by one House-Brackmann grade IV facial nerve palsy and one new pulsatile tinnitus after treatment delivery. All patients without pretreatment deficits remained asymptomatic throughout their follow-up, whereas symptom control and improvement between primarily (91%) and secondarily (94%) treated patients were consistent. The overall LC rate was 99%. One patient developed lymph node metastases 4 months after treatment. The primary tumor lesion was controlled at the time of distant failure. Another patient suffered from a local recurrence (PD) after 70.8 months. The recurrent tumor lesion was treated with proton radiotherapy and is controlled since treatment delivery. At last follow-up, 42 tumors (41%) remained unchanged in size, whereas 57 (56%) showed a TVR. Overall, the median and mean volume reduction were 1.77 and 0.8 cc, respectively. These absolute reductions equal median and mean percentage changes of 22% and 24%, respectively. Paired student's t tests among all, primarily treated and secondarily treated patients showed a significant decrease in tumor volume for the three groups at last follow-up (Table 2). The calculated progression free survival was 97%, 97%, and 93% after 3, 5, and 7 years, respectively. A detailed summary of the treatment results is provided in Table 2.

### 3.3 | Complications and toxicity

Seven patients (7%) showed potential toxicity after treatment delivery. Four reported headaches, vertigo, and nausea. One patient described moderate pain irradiating to the mandibula, neck, and ear on the side of the tumor. All patients were treated with glucocorticoids in an outpatient setting and six of them entirely recovered shortly after. Two patients experienced persistent worsening (House-Brackmann grade IV facial nerve palsy, pulsatile tinnitus). No patient experienced radiation necrosis, seizures, acute bleedings, or radiation-induced malignancies.

**TABLE 2** Tumor volume changes, local control, and clinical outcomes of patients at last follow-up

| **Tumor volume changes (pretreatment vs last follow-up)** | | | | | | |
|---|---|---|---|---|---|---|
| **Patient group** | **Mean reduction (cc)** | **Median reduction (cc)** | **Mean percentage volume reduction (%)** | | **Median percentage volume reduction (%)** | ***P*-value** |
| All patients (n = 101) | 1.77 | 0.80 | 24 | | 22 | <.001 |
| Primary treatment patients (n = 62) | 1.51 | 0.71 | 20 | | 20 | <.001 |
| Secondary treatment patients (n = 39) | 2.19 | 0.89 | 29 | | 27 | .0013 |
| Local control (%) | 99 | | | | | |
| **Clinical outcome of symptomatic patients at last follow-up** | | | | | | |
| Clinical outcome | No symptoms | Symptom improvement | Unchanged | Transient worsening | Symptom worsening | New symptoms |
| Number of patients (n = 96) | 23 | 31 | 35 | 5 | 1 | 1 |
| Primary treatment patients (n = 61) | 14 | 21 | 21 | 4 | 0 | 1 |
| Secondary treatment patients (n = 35) | 9 | 10 | 14 | 1 | 1 | 0 |

*Note:* n = number of patients, cc = cubic centimeter.

## 3.4 | Prognostic factors

Multivariate linear and logistic regression analyses were used to assess prognostic factors for TVR, and symptom improvement, defined as full recovery or pretreatment deficit improvement, as well as toxicity. Pretreatment tumor size was found to be a significant predictor of tumor volume at last follow-up ($F[6, 94]$, $R^2 = 0.31$, $P < .01$). TVR in cc increased by 0.24 cc for each pretreatment cc of tumor (Table 3). None of the analyzed factors including age at treatment delivery, sex, pretreatment and posttreatment tumor volumes, indication, dose, prescription isodose, and number of fractions reached statistical significance for symptom improvement (Table 3). Moreover, no significant factors for the occurrence of toxicity after treatment delivery were found (Table 3). Here, a number of fractions were omitted in the analysis as a dependency among the independent variables in the model was identified.

## 3.5 | Literature review

A total of 29 studies have been identified.[9-37] One study was a multicenter trial with 132 patients and was counted as a separate publication even though parts of the data had already been reported elsewhere. The data were heterogeneous and besides follow-up, doses and LC not standardized. Twenty-one studies out of 29 investigated the use of Gamma Knife (GK), only 8 reported the use of linear accelerator- (LINAC) and CK-based RS. The median and mean follow-up ranged from 9.7 to 132 and 25.4 to 86.4 months, respectively. Most studies (22/29) exclusively reported the use of single-session RS. The median dose used for single-session treatments ranged from 12 to 18 Gy, with the majority utilizing 15 Gy. Most patients were primarily treated with RS (64%, 508/788 patients). Throughout all studies, LC rates between 69% and 100% were reported. The overall LC was 93.6% (725/774 patients), with only a minor difference between GK and LINAC/CK studies (94.2% and 91.6%, respectively). Data reporting for acute and long-term complications, LC, as well as symptom control rates—defined as stable or improved pretreatment deficits—was heterogeneous and prevented inclusion of all studies for exact data calculation. Some authors reported results with varying symptom outcome measurements, whereas other studies analyzed clinical outcomes for each pretreatment deficit separately. Moreover, some studies utilized classification systems like the House-Brackmann score or audiogram results. Symptom control rates after RS varied from 22% to 100% throughout the reviewed studies, with 88.8% of patients achieving symptom control at last follow-up. Complications of RS were reported in 20 out

**TABLE 3** Prognostic factors for tumor volume reduction, symptom improvement, and toxicity by multivariate linear and logistic regression analyses

| **Tumor volume reduction (absolute, in cc)** | | | |
|---|---|---|---|
| **Factor** | **Coefficient** | ***P*-value** | **95% confidence interval** |
| Age | −0.12 | .53 | −0.05-0.27 |
| Sex | 0.91 | .12 | −0.26-2.10 |
| Pretreatment tumor volume | 0.24 | <.01 | 0.15-0.33 |
| Indication | −1.05 | .07 | −2.20-0.09 |
| Dose | −0.13 | .46 | −0.48-0.22 |
| Isodose | 0.95 | .44 | 0.85-1.07 |
| Fractions | −0.05 | .93 | −1.24-1.14 |
| **Symptom improvement** | | | |
| Factor | Odds ratio | *P*-value | 95% confidence interval |
| Age | 1.00 | .68 | 0.97-1.04 |
| Sex | 1.32 | .58 | 0.48-3.57 |
| Posttreatment tumor volume | 1.03 | .76 | 0.95-1.12 |
| Indication | 0.89 | .82 | 0.33-2.14 |
| Dose | 1.06 | .69 | 0.78-1.44 |
| Isodose | 0.92 | .30 | 0.80-1.06 |
| Fractions | 0.62 | .40 | 0.20-1.88 |
| Toxicity | | | |
| Age | 0.95 | .14 | 0.89-1.01 |
| Sex | 1.37 | .72 | 0.23-7.89 |
| Pretreatment tumor volume | 1.01 | .34 | 0.91-1.14 |
| Indication | 0.57 | .51 | 0.10-3.03 |
| Dose | 0.66 | .16 | 0.37-1.18 |
| Isodose | 1.07 | .49 | 0.87-1.30 |

*Note:* Sex represents male vs female; indication represents primary vs secondary treatments; cc represents cubic centimeter.

of 29 studies (68%) with complication rates ranging from 2% to 28% in treated patients. The nine studies without reporting complications had only 20 or fewer patients included. Overall, 8.8% (70/788 patients) experienced toxicity and complications after treatment delivery, with a slightly higher rate found in LINAC/CK studies (12.7% and 7.9%, respectively), which might be explained by the larger tumor volumes treated in LINAC/CK studies (Table 4). A summary of the literature review is provided in Table 4.

## 4 | DISCUSSION

Herein, we report the first multicenter study on the role of image-guided RRS in the management of GJTs and the second-largest published radiosurgical series of patients treated for GJTs. The results demonstrate that RRS achieves high rates of tumor and symptom control throughout an intermediate follow-up time. These findings are consistent for primarily and secondarily treated GJTs patients. Moreover, acute complications after treatment delivery are rare and no treatment-related mortality has been observed.

### 4.1 | Local control

As GJT recurrence can occur even after decades, long-term follow-up is needed to determine if our initially reported LC with this sample size is reliable and lasting.[5,38,39] Many reports showed radiosurgical LC rates over 90% with an even more extensive follow-up period.[12,14,19,20,24] Of these studies, Sheehan and colleagues published the first multicenter RS study for GJT with the data of the North American Gamma Knife Consortium. To date, it is the most extensive radiosurgical series available. They included 132 patients with 134 GJTs

**TABLE 4** Literature review

| Author | Number of patients | Modality | Primary Tx (number of patients) | Secondary Tx (number of patients) | Follow-up time (months) | Tumor size (cc) | Fx | Dose (Gy) | LC (%) | Symptom control (%) | Complications and toxicity (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tripathi et al, 2019[9] | 10 | GK | 10 | 0 | Mean: 39 | Mean: 29.9 | 2-3 | 2 fractions mean: 11.2, 3 fractions mean: 7.64 | 100 | 100% | Two patients (20%), one with spinal accessory nerve palsy, one with headache. |
| Gigliotti et al, 2018[10] | 16 | LINAC | 10 | 6 | Median: 44 | Median: 11.7 | 1-5 | Median: 25 | 88 | 81.2 | Two patients (12.5%), one with vertigo, one with headache. |
| Sallabanda et al, 2018[11] | 30 | LINAC, CK | 14 | 16 | Mean: 55.2 | Median: 56 | 1-3 | Median: 14.0 | 97 | 97 | Four patients (13.3%) with low-grade toxicities. |
| Hafez et al, 2018[12] | 40 | GK | 40 | 0 | Mean: 84 | Mean: 6.5 | 1 | Mean marginal: 15.0 | 92 | 92.5 | Three patients (7.5%) with new cranial nerve deficits. |
| Sharma et al, 2018[13] | 42 | GK | 30 | 12 | Median: 62.3 | Mean: 5.0 | 1 | Median marginal: 15.0 | 69 | 80.9% | Eight patients (19%) with low-grade toxicities. |
| Patel et al, 2018[14] | 60 | GK | 35 | 25 | Median: 66 | Median: 11.6 | 1 | Mean maximal: 32, mean marginal: 16 | 91.7 | 96.6 (hearing data excluded) | Two patients (3.3%) with vocal cord paralysis. |
| Ibrahim et al, 2017[15] | 75 | GK | 47 | 28 | Median clinical: 38.5, median radiographic: 51.5 | Median: 7.0 | 1-2 | Median marginal: 18 | 93.4 | 84 | Two patients (2.6%), one with vocal cord paralysis, one with facial nerve palsy. |
| Wakefield et al, 2017[16] | 17 | GK | 8 | 9 | Median: 123 | Median: 9.8 | 1 | Median: 15.0 | 94 | 94 | None. |
| Winford et al, 2017[17] | 38 (33 with follow-up imaging) | GK | 34 | 4 | Mean radiographic: 39.1 | Median: 5.8 | 1 | Mean marginal: 13.2 | 88 | 94 for patients with pretreatment nerve deficits | Total of 10 patients (26.3%), four with vertigo, four with pain, two with transient taste disturbance, two with dysphagia, one with necrosis. |
| Dobberpuhl et al, 2016[18] | 12 | GK | 12 | 0 | Mean: 27.6 | Median: 8.4 | 1 | Median marginal: 15 | 100 | 100 for lower cranial nerve palsies, 66.7% for pulsatile tinnitus | None. |
| El Majdoub et al, 2015[19] | 27 | LINAC | 13 | 14 | Median clinical: 132, median radiographic: 115 | Median: 9.5 | 1 | Median: 15 | 100 | 96.2 | One patient (3.7%) with a persistent facial nerve palsy. |
| Gandía-González et al, 2014[20] | 58 | GK | 40 | 18 | Mean: 86.4, median: 76.6 | Median: 9.3, mean: 12 | 1 | Mean maximal: 25.2, mean marginal: 13.6 | 94.8 | 91.4 | Two patients (3.4%) with new hearing loss. |
| Sager et al, 2014[21] | 21 | LINAC | 16 | 5 | Median: 49 | Median diameter: 17 mm | 1 | Median: 15 | 100 | 22 to 62.5, depending on pre-clinical deficits | Six patients (28.5%), two patients with nausea, vomiting, headache, three patients with transient facial numbness, one patient with tongue weakness. |
| Hurmuz et al, 2013[22] | 14 | CK | 13 | 1 | Median: 39 | Median: 15.8 | 1-5 | Median: 25 | 100 | NR (8 patients with complete clinical improvement) | None. |
| De Andrade et al, 2013[23] | 15 | LINAC | 13 | 2 | Mean: 35.4 | Mean: 18.5 | 1-5 | Mean marginal: 14 | 100 | 100 | One patient (6.6%) with transient facial nerve palsy. |
| Sheehan et al, 2012[24] | 132 (123 with follow-up imaging) | GK | 75 | 57 | Median: 50.5 | Median: 5.5, mean: 7.8 | 1 | Median: 15 | 93.0 | 85 for cranial nerve deficits | Fifteen patients (11.3%) with worsening cranial nerve deficits despite tumor control. |
| Chen et al, 2010[25] | 15 | GK | 11 | 4 | Mean: 43.2 | Mean: 7.3 | 1 | Mean marginal: 14.6 | 80.0 | 88.8 | One patient (6.6%) experienced worsening dysarthria, dizziness, and headache. |
| Genç et al, 2010[26] | 18 | GK | 7 | 11 | Median: 41.5, mean: 52.7 | Median 5.54, mean 13.5 | 1 | Mean marginal: 15.6 | 94.4 | 94 | None. |
| Navarro Martín et al, 2010[27] | 10 | GK | 2 | 8 | Median: 9.7 | Median: 4.0 | 1 | Median marginal: 14.0 | 100 | 100 | None. |
| Ganz & Abdelkarim, 2009[28] | 14 | GK | 11 | 3 | Mean: 28 | Mean: 14.2 | 1 | Mean: 13.6 | 100 | 100 | One patient (7.1%) with transient facial nerve palsy. |
| Miller et al, 2009[29] | 5 | GK | 0 | 5 | Mean: 34 | Mean: 4.14 | 1 | Mean marginal: 15.0 | 100 | 100 | None. |
| Sharma et al, 2008[30] | 13 | GK | 7 | 6 | Mean: 25.4 | Mean: 5.7 | 1 | Mean marginal: 16.5 | 100 | Symptom improvement in 46% of patients with ≥6 months of follow-up. | One patient (7.6%) with trigeminal neuralgia. |
| Lim et al, 2007[31] | 18 | LINAC, CK | 14 | 4 | Median clinical: 35, median radiographic: 30 | Mean diameter: 3.04 cm | 1-3 | Median: 20 | 100 | 100 | Three patients (16.6%) experienced transient worsening of cranial nerve deficits. |
| | 16 | GK | 5 | 11 | Median: 18.5 | Median: 9.8 | 1 | | 100 | 100 | None. |

(Continues)

**TABLE 4** (Continued)

| Author | Number of patients | Modality | Primary Tx (number of patients) | Secondary Tx (number of patients) | Follow-up time (months) | Tumor size (cc) | Fx | Dose (Gy) | LC (%) | Symptom control (%) | Complications and toxicity (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bitaraf et al, 2006[32] | | | | | | | | Median marginal: 18.0 | | | |
| Feigl & Horstmann, 2006[33] | 12 | GK | 7 | 5 | Mean: 33 | Mean: 9.4 | 1 | Mean marginal: 17.0 | 100 | 92 | Two patients (16.6%), one with transient facial spasm, one with transient hoarseness. |
| Gerosa et al, 2006[34] | 20 | GK | 12 | 8 | Mean: 50.8 | Mean: 7.03 | 1 | Mean marginal: 17.3 | 100 | 90 | None. |
| Poznanovic et al, 2006[35] | 8 | LINAC | 8 | 0 | Mean: 15.6 | Mean: 7.2 | 1 | Median: 15.0 | 100 | 87.5 | Two patients (25%), one patient experienced acute vertigo, one patient suffered from acute nausea, vomiting and transient cranial nerve neuropathy. |
| Eustacchio et al, 2002[36] | 19 | GK | 10 | 9 | Median: 86.4 | Median: 5.22 | 1 | Median marginal: 14.0 | 94.7 | 100 | None. |
| Saringer et al, 2001[37] | 13 | GK | 4 | 9 | Mean: 50 | Mean: 9.03 | 1 | Median marginal: 12 | 100 | 100 | Two patients (15.3%), one with transient dysphagia and one with facial nerve palsy. |
| Modality | Number of studies | Number of patients | Primary Tx (number of patients, %) | Secondary Tx (number of patients, %) | Follow-up time range (median and mean, months) | Tumor size range (median and mean combined, cc) | Fx (median, range) | Dose (median and mean marginal combined, Gy) | LC (%, patients with follow-up imaging available) | Symptom control (%, only overall reported deficits included) | Complication and toxicity rate (%) |
| All | 29 | 788 | 508 (64.4%) | 280 (35.6%) | 9.7-132 | 4-56 | 1, 1-5 | 11.2-25 | 93.6 (725/774) | 88.8 (442/498) | 8.8% (70/788) |
| GK | 21 | 639 | 407 (63.7%) | 232 (36.3%) | 9.7-123 | 4-29.6 | 1, 1-3 | 11.2-18 | 94.2 (593/629) | 86.9 (334/384) | 7.9% (51/639) |
| CK, LINAC | 8 | 149 | 101 (67.8%) | 48 (32.2%) | 15.6-132 | 7.2-56 | 1, 1-5 | 14-25 | 91.6 (132/149) | 94.7 (108/114) | 12.7% (19/149) |

Abbreviations: cc, cubic centimeter; CK, CyberKnife; Fx, number of fractions; GK, Gamma Knife; LC, local control; LINAC, linear accelerator; mm, millimeter; NR, not reported; Tx, treatment.

from eight institutions and reported progression-free survival (PFS) rates of 98%, 90%, and 88% at 1, 3, and 5 years, respectively.[24] The actual LC was 93% at a median follow-up of 50.5 months.[24] Five-year LC rates around 90%-95% seem to be achievable with RS (Table 4). Similar PFS rates have been reported.[14,15,24] Moreover, recent studies including this report have investigated prognostic factors for LC or tumor progression-free survival.[11,13,15,17,20,24]

Sheehan and colleagues found significant factors in their multivariate analysis. In their study, a higher number of isocenters and the absence of trigeminal nerve dysfunctions at the time of treatment delivery were associated with progression-free tumor survival.[24] Also, Winford and colleagues identified an increased risk of progression with increased margin treatment doses.[17] Herein, we found that pretreatment tumor volume significantly influences posttreatment tumor size changes. However, identifying prognostic factors remains a difficult task given the rarity and delay of local recurrences. Such factors might unmask with more extensive follow-up periods and more detailed as well as structured patient assessments. We expect to see more recurrences in our study cohort within the next years.

Besides, the present LC rates for primary and secondary GJT treatments are comparable with the radiosurgical data available, even though most of the data is from GK-based studies due to the availability and history of this radiation technique (Table 4). Past studies have used various definitions of tumor progression, which might compromise comparability. This effect can also be increased by varying tumor volume measurement methods. Given the provided study data and reviewed literature, there seem to be no significant differences in LC in regard to the radiosurgical treatment modality (GK, LINAC, and CK) and number of fractions. Past surgical series might have focused on peripheral GJTs, including those extending to the lower neck. Therefore, comparing our findings with surgical series is challenging due to heterogeneous patient selection and different surgical techniques. LC seems to be at least similar or slightly better for radiosurgical patients compared with surgery.[5,7] Large surgical series with more than 60 patients included report LC rates between 76% and 93%.[5,7,40-42] Ultimately, authors have argued that only a full surgical resection may achieve complete cure.[7] Nevertheless, not all studies provide sufficient details regarding the follow-up time, hindering comparability between RS, fractionated radiotherapy and surgery. Furthermore, the data heterogeneity of GJT patients in past studies makes it difficult to determine patients who would benefit from primary microsurgical resection or fractionated radiotherapy, especially considering recent advancements in surgery

and cranial nerve management.[43,44] Besides, fractionated radiotherapy has shown to achieve comparable LC rates and may play an important role for patients not suitable for RS.[5,7] Here, doses up to 45 Gy achieve good clinical results with a limited risk of adverse effects.[7]

Even though treatment guidelines including surgical and radiosurgical options have been proposed by colleagues, consensus guidelines for the treatment of GJT are still lacking.[5,7] Still, surgical tumor resection is a treatment option which must be considered, especially for rapidly growing and hormone-secreting tumors. Moreover, some authors emphasized on a more passive approach and suggested to follow a "wait and scan" strategy more frequently.[45] This option is also supported by data showing that even throughout an extensive follow-up of more than 5 years, 45% of patients experience tumor stability or regression without treatment.[45,46] Finally, radiobiological studies suggest paragangliomas to be relatively radioresistant given the expression of known markers of radioresistance (NOTCH, ZEB1) and down-regulation of cellular pathways fostering radiosensitivity (miR-200c, mir-34b/c).[47-49] This might support a more passive treatment approach. Overall, the decision for treatment must be carefully evaluated and in agreement with the patient's preferences, clinical status and personal wishes.

## 4.2 | Symptom control and quality of life

GJTs often account for considerable morbidity and significantly impact the quality of life (Qol).[50] Thus, patient-reported outcomes and projected symptom control are crucial when determining the most suitable treatment option for patients besides overall performance status and patients' preferences. In this study, 93% of the treated patients, regardless of undergoing primary or secondary RRS, experienced symptom control or improvements in their pretreatment deficits. Considering the sample size and follow-up time, this proportion underlines the effectiveness of RRS and demonstrates the equivalence in regard to GK-based treatments (Table 4). However, reported data are heterogeneous and some authors examined the changes in pretreatment deficits for every symptom separately as well as used quantitative assessments like audiograms. Most studies analyzed in our literature review reported symptom control rates of ≥80%, with an estimated overall rate of 88.8% (442/498 patients, Table 4). Notably, these rates were mostly consistent regardless of sample size, tumor volume, follow-up period and radiation modality (Table 4). Thus, RS achieves reliable clinical results, especially in contrast to most invasive treatments. Surgery, despite achieving comparable LC rates, still yields a considerable risk for persistent or newly developing cranial nerve palsies, thus, limiting the chances of symptom control.[5,7] However, less invasive surgical methods seem to lower the rate of newly developing postsurgical cranial nerve deficits.[43,44]

Today, variables indicating clinical outcomes are still lacking. Various reports including this study investigated prognostic factors for symptom control or clinical progression-free survival after treatment.[11,15,16,20] Sallabanda and colleagues found cranial nerve involvement to be significantly associated with a decreased chance of symptom improvement.[11] However, the association was apparent in univariate analysis, a multivariate analysis was not conducted. Besides, Wakefield and colleagues found prior surgical resection to significantly correlate with persistent neurological deficits compared with non-surgical cases.[16] In contrast, our study found no prognostic factors for symptom improvement. Besides reporting subjective symptom control, analyses of standardized Qol measurements before and after treatment could improve clinical decision making. However, only sparse standardized Qol data are available in the GJT literature.[51-53] Galland-Girodet and colleagues found better scores for hearing and speech, trismus, and overall Qol for patients with head and neck paragangliomas receiving radiotherapy alone vs those receiving radiotherapy and surgery.[51] Patel and colleagues investigated Qol outcomes for primary and secondary GJT patients after GK-based RS.[52] Patients undergoing primary RS had better swallowing function than patients who underwent surgical resection before.[52] One study investigating fractionated radiotherapy showed stable SF36 Qol measures for patients undergoing primary radiotherapy.[53] Finally, a recent single center study utilizing pretreatment and posttreatment SF12 data showed consistent Qol improvements after RRS.[54] Overall, these findings suggest that RS and radiotherapy seem to be favorable in regard to post-treatment Qol in comparison with surgery. Despite the lack of data and sufficient studies, projected Qol outcomes after treatment should play an important role when choosing the right treatment modality.

## 4.3 | Complications and toxicity

In addition, complications and treatment-related morbidity are linked to the clinical outcome of patients and have a significant impact on clinical decision making. In our study cohort, only a few transient low-grade and persistent complications have been observed. This is also in agreement with the existing literature (Table 4). Complication rates for RS range from 0% to 28%; most of the studies (62%) had rates below 10%, with an overall rate of

8.8% throughout all studies. Our complication rate (7%) is in agreement with the reviewed literature. Most complications were low grade, ranging from nausea, vertigo, headaches to transient cranial nerve deficits, and resolved after a short amount of time. However, we were not able to find predictors of toxicity in regard to applied doses. Given the low rate of complications after RS, the majority of other studies have not investigated the relationship between dose and toxicity. However, most of the GJTs have been treated with doses around 16 Gy and low-grade complications occurred in less than 10% of patients (Table 4).

In contrast to surgery, RS has an advantageous complication profile with a lower risk, especially for posttreatment cranial nerve deficits.[5,7] Fractionated radiotherapy seems to have a slightly higher risk for complications, 10.4% and 6.5%, respectively.[7] In contrast, complications after surgery are much more frequent and severe. A review by Lieberson and colleagues reported complication rates of ≥46% after surgery.[5] Suárez and colleagues reported major complications including CSF fistulas, aspirations, infections, meningitis, strokes, and death in 28% of surgical cases.[7] These reviews underline the considerable complication risk for gross GJT resections. Even though the risk for radiation-associated long-term complications like radiation-induced malignancies is low, RS should be especially considered for older patients. Overall, candidates for GJT treatment should be well-informed about the potential complications and toxicity of RS, fractionated radiotherapy and surgery.

## 4.4 | Limitations

This study has various limitations. The retrospective nature, due to selection and reporting biases, is an inheriting limitation of the study and as most of the included patients underwent RS as their primary GJT treatment, histological confirmation was only performed in 39 out of 101 patients. Nevertheless, the radiological diagnosis is considered reliable and accurate, often because of a characteristic contrast enhancement and especially in conjunction with typical symptoms of GJTs and modern imaging modalities (CT, MRI, and CE-MRA).[55-58] In regard to the literature and tumor biology of GJTs, the follow-up time of our study is too short to detect late tumor recurrences reliably. These can occur even decades after treatment delivery.[5,8,38,39] While our initially reported LC is high, we expect to see more and more local recurrences five or more years after treatment delivery. Moreover, our PFS might be too high given insufficient return of patient information regarding deaths by any cause. This might be especially the case for outpatient only treatment facilities and centers. Finally, we only reported the qualitative data for our posttreatment symptom analyses in this study and did not provide audiograms or House-Brackmann scores. This circumstance might limit the validity of our posttreatment symptom results. However, many of the published studies have used this way of reporting to depict their findings.

## 4.5 | Current and future challenges

So far, only limited progress has been made in evaluating multimodal and interdisciplinary treatment options despite the amount of retrospective reports. RS has shown at least equal to favorable results compared to fractionated radiotherapy and surgical series in regard to LC, symptom control and toxicity over the past decades.[5,7] However, reporting heterogeneity, patient selection and technical advancements in all fields warrant a more detailed and comprehensive analysis. It is essential to conduct more studies on the primary and secondary treatment of GJTs and to evaluate multidisciplinary treatment options critically. Comparative studies, ideally of prospective nature, could help to establish treatment guidelines and determine which patients could potentially benefit from surgical resection or fractionated radiotherapy. Currently, there is a lack of knowledge on how to maximize symptom control and posttreatment Qol. A prospective international multicenter study with standardized outcome evaluations including audiograms, video-head impulse tests, caloric vestibular tests, extensive lower cranial nerve testing, and Qol assessments could overcome the epidemiologic challenges and improve clinical care for GJT patients. Moreover, such a study should follow an interdisciplinary approach and include the expertise of neurosurgeons, neurologists, radiation, and otolaryngologist. Yet, it is important to note that the various treatment options available, the variety of patients in regard to neurological deficits, pretreatments, and tumor size as well as the low tumor incidence pose considerable challenges to conduct prospective trials. In addition, radiosurgical and multidisciplinary treatment options for other paragangliomas should be investigated as well and may be included in one large prospective trial. Considering our findings, similar long-term experiences with GK, and the possibility to treat extracranial lesions, RRS may be suitable for the treatment of other head and neck paragangliomas than GJTs.[59]

# 5 | CONCLUSION

This multicenter study is the largest series investigating the use of RRS for GJTs and, overall, the second-largest radiosurgical series for the treatment of GJTs. Results

show that RRS is a well-tolerated and effective treatment modality that achieves high LC rates and improvement in pretreatment deficits regardless of primary or secondary treatment delivery. This is in agreement with the radiosurgical literature. RRS and RS in general may be a suitable treatment modality for the majority of GJTs.

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## CONFLICT OF INTEREST

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## ORCID

*Felix Ehret* https://orcid.org/0000-0001-6177-1755

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