Stereotactic radiosurgery of glomus jugulare tumors: current concepts, recent advances and future perspectives

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Practice points

- Stereotactic radiosurgery (SRS) is a relatively new treatment concept for glomus jugulare tumor (GJT) management; however, there is now nearly two decades of experience, and compiling data from studies with longer follow-up durations support the utility of SRS as a safe and effective therapeutic option.
- Recent advances in SRS include improvements in neuroimaging, radiation treatment techniques, equipment, treatment planning and delivery systems.
- Gamma knife technology is now capable of extended anatomical reach, which may allow for treating some GJT below the skull base.
- Fractionated stereotactic treatments with the Gamma knife technology has been possible by use of noninvasive, relocatable cranial immobilization systems, which enable the treatment of larger GJT whilst exploiting the high mechanical accuracy of Gamma knife radiosurgery.
- Although experience with linear accelerator-based systems for GJT radiosurgery is more limited, currently available data show comparable safety and efficacy.
- Combination of SRS and antiangiogenic agents, and the utility of proton beam SRS for GJT management merit active investigation.

SUMMARY Stereotactic radiosurgery (SRS), a very highly focused form of therapeutic irradiation, has been widely recognized as a viable treatment option in the management of intracranial pathologies including benign tumors, malign tumors, vascular malformations and functional disorders. The applications of SRS are continuously expanding thanks to the ever-increasing advances and corresponding improvements in neuroimaging, radiation treatment techniques, equipment, treatment planning and delivery systems. In the context of glomus jugulare tumors (GJT), SRS is being more increasingly used both as the upfront management modality or as a complementary or salvage treatment option. As its safety and efficacy is being evident with compiling data from studies with longer follow-up durations, SRS appears to take the lead in the management of most patients with GJT. Herein, we address current concepts, recent advances and future perspectives in SRS of GJT in light of the literature.

Glomus jugulare tumors (GJT) are rare tumors arising within the paraganglionic tissue of the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve) or auricular branch of the vagus nerve (Arnold's nerve). First descriptions of glomus tissue date back to 1840, and the term 'glomus jugulare' was coined about one century later by Guild to define the small structure within the adventitia of the jugular bulb in the middle ear [1–4]. GJT generally follow an indolent clinical course with a low

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growth rate, which may justify a wait-and-scan approach in selected patients [5,6]. Nevertheless, although an overwhelming majority of GJT are benign with low metastatic potential [7], symptoms may arise as a consequence of the mass effect and/or local invasion of adjacent neurovascular structures including the jugular bulb, internal carotid artery and lower cranial nerves which warrant management. Affected patients may suffer from symptoms including hearing loss, otalgia, pulsatile tinnitus, vertigo, dizziness, headache and dysphagia which significantly deteriorate their quality of life.

Detailed history and physical examination along with imaging studies are useful in clinical diagnosis of GJT. While high-resolution computed tomography (CT) primarily provides information about bone extension, MRI is used to assess soft tissue borders of the tumor, multicentricity, tumor vascularity and extension along neural foramina.

Since GJT may have inherited forms, genetic testing may be offered [8]. Succinate dehydrogenase mutations have been shown to be associated with hereditary paragangliomas [9]. Familial forms of GJT typically display distinct clinical features such as presenting at earlier ages, being multicentric and more aggressive with a higher propensity for metastatic spread. In this aspect, genetic testing may have a role in management [10,11]. Screening for succinate dehydrogenase mutations to identify high-risk individuals may allow for earlier detection of GJT when they are limited, which may have implications for earlier management with potentially decreased treatment morbidity.

Surgical resection with or without preoperative embolization and radiation therapy are among the therapeutic options for GJT management. Radiation therapy may be delivered as either conventionally fractionated radiotherapy or high-precision radiosurgery in the form of stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy.

Surgery has been traditionally used as an effective treatment modality in the management of GJT with the primary advantage of offering immediate tumor elimination. Lesions causing symptoms due to brainstem compression are managed best with surgery, which provides immediate decompression leading to resolution of symptoms from the mass effect. Also, surgery may be used as part of a tailored approach to minimize morbidity of treatment

[12–16]. Particularly for elderly patients, limited surgical resection followed by SRS to residual GJT may offer improvement in pulsatile tinnitus and residual hearing without significant toxicity [14–16]. However, insidious onset of symptoms frequently precludes early detection of GJT, thus the lesions may be quite large and not amenable to complete surgical removal at the time of diagnosis. Moreover, the critical location of GJT in a poorly accessible surgical region of the skull base highlights the need for vigilance in management with invasive therapeutic options. From the standpoint of neurosurgery, GJT are considered as one of the most challenging lesions in the skull base due to their intimate association with major neurovascular structures. The hypervascular nature of these tumors further complicates surgical management. Despite advances in surgery [17,18], extensive resection of GJT has great potential to leave the patients with substantial treatment-related morbidity, which should be considered as a high cost for the management of a mostly benign tumor [19–21].

Suárez *et al.* recently conducted a comprehensive literature review including 69 eligible studies to assess the surgical and radiotherapeutic management of jugular and vagal paragangliomas [21]. Local control rate was higher with SRS compared to external beam radiation therapy and surgery (local control rate 93.7% with SRS vs 89.1% with external beam radiation therapy, and 78.2% with surgery). While SRS was not associated with any deaths, mortality rates secondary to surgery and external beam radiation therapy were 1.6 and 2%, respectively. The most significant difference between surgery and radiotherapy was in morbidity outcomes. While surgery increased cranial nerve palsies by 181.6% compared to preoperative levels, SRS and external beam radiation therapy decreased cranial nerve palsies by 8.8 and 4.1%, respectively. Based on the retrospective data, radiation therapy has been shown to achieve more favorable outcomes in terms of local control and morbidity in patients with jugular paragangliomas [21].

In another recent report by Lieberman *et al.* [22], analysis of 41 studies including 1310 patients revealed that surgery was associated with significantly higher rate of major complications, higher number of cranial nerve palsies and lower tumor control compared to radiotherapy or radiosurgery. Overall local control with SRS was 98% at a mean follow-up of approximately

31 months (range: 1–193 months). Again, based on the retrospective data, considering surgery for only selected patients was suggested [22].

In the meta-analysis by Guss *et al.* [23] assessing the outcomes of radiosurgery for GJT, tumor control was 97% and clinical control was 95% based on data from 19 studies with 335 patients. When the analysis was limited to studies with a mean or median follow-up time exceeding 36 months, tumor control was 96% and clinical control was 95%. Considering radiosurgery for the primary management of GJT was suggested [23].

Ivan *et al.* [24] conducted a meta-analysis of studies totaling 869 patients treated with surgery and/or SRS to evaluate tumor control rates and treatment-related morbidity for patients with GJT. Tumor control rate was highest (95%) for patients undergoing SRS at a mean follow-up time of 71 months. Morbidity outcomes were also more favorable for SRS, and the authors underscored the importance of SRS in the management of GJT [24].

Given the potential risks of extensive surgery, radiation therapy has been suggested as a complementary or alternative management strategy particularly for elderly patients with unresectable, incompletely resected, or recurrent GJT. Conventionally fractionated external beam radiation therapy has been used as a viable therapeutic option in the management of patients with extensive GJT in particular. Most recent series using a median dose of 45 Gy in 25 fractions report excellent local control rates with a favorable toxicity profile, and considering conventionally fractionated external beam radiation therapy as a first-line treatment of choice is even suggested [25,26].

While conventionally fractionated radiation therapy has a longer history in GJT management, inclusion of SRS in the therapeutic armamentarium dates back to mid-1990s [27,28]. Thus, nearly 2 decades of experience with GJT radiosurgery is currently available. During this time span, SRS has led to a paradigm shift with breakthroughs in technology and corresponding improvements in neuroimaging, radiation treatment techniques, equipment, treatment planning and delivery systems. Technological advances coupled with the adopted concept of minimally invasive modern neurosurgical approaches have expanded the spectrum of SRS from the standpoint of both radiation oncology and neurosurgery disciplines. Radiosurgical applications currently constitute a considerable

part of neurosurgical practice in major departments of neurosurgery [29]. SRS has gained great popularity and supplanted conventional radiation therapy in many centers worldwide. Several studies have addressed the utility of GJT radiosurgery using the platforms of Gamma knife, Cyber knife and other linear accelerator (LINAC)-based systems. Promising treatment outcomes with a favorable risk to benefit ratio even led to consideration of this modality for primary management of GJT [22,23,30].

GJT may be considered as ideal targets well-suited to SRS since they are usually visualized with well-defined limits. This allows precise target localization for stereotactically focused high-dose irradiation with steep dose gradients around the lesion. The effect of SRS is probably through induction of endothelial inflammation, apoptosis, vascular endothelial damage and fibrosis around tumor-supplying vessels leading to tumor control [31,32]. Current image guidance technologies further refine treatment precision, which may potentially improve normal tissue sparing. Indeed, the primary advantage of SRS appears to be its improved toxicity profile compared to surgical treatment [21–24]. Shortening of overall treatment time and recovery as an outpatient procedure, earlier return to daily life, improved functional preservation and quality of life, fewer procedure-related morbidity and mortality may be considered among the favorable aspects of radiosurgical management. Moreover, considering the complexity of surgery for GJT, SRS may be advantageous from the standpoint of cost-effectiveness, which is supported by data from comparative cost analyses for other indications [33,34].

While SRS techniques are currently capable of utilizing different types of radiation including heavy charged particles and protons, photon irradiation is more commonly used partly due to widespread availability with easier access and lower cost. Major platforms for GJT radiosurgery include the Gamma knife, Cyber knife and other LINAC-based systems all of which have been shown to achieve favorable treatment outcomes [21–24,27,28,30,35–67]. The recognition of SRS as a viable treatment modality has prompted continual development of novel technologies providing higher speed, comfort and precision. Besides camaraderie, competition among vendors in the market has contributed to rapid evolution of techniques with decreased costs, rendering SRS a more appealing therapeutic option. Most of the

experience with GJT radiosurgery comes from studies using the Gamma knife due to its longer therapeutic history [35–40,42–47,51,52,56–59,61,62,67]. Indeed, LINACs were not originally designed to perform SRS; however, their modification and adaptation for SRS with high treatment precision comparable to the Gamma knife technology has enhanced the popularization of radiosurgical technique [68]. With various platforms available for radiosurgery, basic concept remains the same for all: delivering high doses of radiation to the target whilst sparing normal tissues with a steep dose fall-off by means of stereotactic localization, computerized treatment planning and a precise radiation delivery system [69–71].

While the individualized treatment decision for a given patient with GJT should take into account many factors including patient preference, age, comorbidities and overall performance status, tumor size, localization, evidence of persistent growth, symptomatology and a thorough assessment of risk-to-benefit ratio for available management options, we herein address briefly the recent advances in SRS which render it a more attractive therapeutic option.

Evolution of Gamma knife systems

Model C version of the Gamma knife introduced in 1999 had the capability of using robotic positioning to set treatment coordinates, which helped rapid execution of multiple-isocenter treatment plans. Model 4-C version introduced in 2004 came up with some refinements to improve workflow, enhance precision and support integrated imaging systems.

The cutting-edge technology Leksell Gamma knife Perfexion (Elekta AB) was introduced in 2006. It contains 192 cobalt-60 sources arranged in conical configuration and offers improved shielding capability and flexibility. An improved automatically controlled collimator setting is available. Collimator has eight sectors which provide separate beam diameters of 4, 8 and 16 mm, along with the beam block position [72]. This high-end model allows the generation of highly sophisticated conformal treatment plans adjusting to lesion's shape by making possible the mixture of different collimator sizes. While creating ellipsoid fields is enabled by use of combining different collimator sizes, it is also now possible to treat some GJT lesions located below the skull base by virtue of a larger patient aperture. The larger patient aperture minimizes the need for patient repositioning and frame shifting. Entire

bed moving for patient positioning improves comfort. MR to CT fusion errors are eliminated by use of MR-compatible frames. Besides its capability of extended anatomical reach, Leksell Gamma knife Perfexion has been shown to improve efficiency without compromising conformality [73]. Reduction in setup time has great potential to improve workflow in busy centers, which is an important advantage. Improved accuracy and reduced extracranial doses are among the other favorable aspects of this latest version [72].

While Gamma knife radiosurgery has traditionally been a single-session treatment, the introduction of relocatable immobilization systems has made multifraction or serial multisession treatments possible. Feasibility and accuracy of using a relocatable frame system for fractionated Gamma knife radiosurgery was recently reported [74]. This approach may allow for treating larger GJT whilst exploiting the high mechanical accuracy of Gamma knife radiosurgery [75,76].

Dose escalation may be considered in fractionated regimens in an attempt to attain maximal therapeutic gain. Clearly, image guidance is crucial for accurate positioning and immobilization of patients undergoing stereotactic irradiation. Sophisticated systems integrated with dedicated Gamma knife radiosurgery units eliminate the need for invasive head fixation and achieve excellent image guidance, which may further improve the accuracy of treatments [77]. Major advantages of using noninvasive, relocatable cranial immobilization systems include improved patient comfort, flexibility in designing treatment schedules, and additional time for optimal simulation, planning and quality assurance on treatment days. Several studies have reported the accuracy of immobilization with noninvasive, relocatable cranial immobilization systems designed for fractionated intracranial radiosurgery [74,77,78]. A very recent study evaluating the geometric accuracy of automated positioning system in Gamma knife radiosurgery has revealed that total spatial uncertainties were acceptable for clinical use [79]. Gamma knife radiosurgery will probably prove to be a useful tool in the management of some GJT below the skull base by virtue of its extended anatomical reach. Gamma knife technology has come a long way since its inception with its improved efficiency, accuracy, enhanced anatomical reach, decreased extracranial doses and capability to allow fractionated stereotactic treatments by use

of relocatable noninvasive immobilization systems. Favorable treatment outcomes of Gamma knife radiosurgery for GJT will probably be further refined in the near future thanks to the recent advances.

Evolution of LINAC-based systems

LINAC-based systems including XKnife (Radionics Inc., MA, USA), Novalis Tx (BrainLAB AG, Germany and CA, USA), the Peacock System (NOMOS Corp., PA, USA), Tomotherapy Hi-Art (TomoTherapy, Inc., WI, USA), Cyber knife (Accuray, Inc., CA, USA) and several other modernized LINAC technologies capable of performing high-precision SRS serve as viable alternatives to the Gamma knife technology with improved hardware and advanced dose planning software. An advantage of LINAC-based systems is their capability to treat GJT located both above or below the skull base. Higher mechanical flexibility with a greater field size enables treatment of patients with GJT located below the skull base. Moreover, stereotactic body radiation therapy, a relatively newer concept, offers the capability of treating multiple extracranially located glomus tumors in a single session.

The introduction of micro-multileaf collimators (mMLC) has been a major advance for LINAC-based radiosurgical systems. Before the invention of mMLC, radiation beams generated by LINAC had a circular cross-section and treatment of tumors with irregular shapes was more difficult. By virtue of mMLC with smaller leaf sizes of 2–5 mm, more precise shaping of irregular fields (as in the case of GJT) and achieving improved geometric accuracy for SRS treatments have been possible. The ‘beam’s eye view’ concept allows excellent conformity of the beam to the lesion, and improves treatment precision. The implementation of dynamic conformal arc therapies has been possible with the treatment apertures changing with respect to target and critical structure localizations. Also, intensity modulation has been possible by changing the fluency within the treatment fields. With the ability to use inverse planning approaches for SRS, there is potential for achieving improvements in the quality of plans at shorter planning times. The implementation of Volumetric Modulated Arc Therapy with image guidance may serve as a tool to achieve improved treatment outcomes in terms of decreased toxicity and treatment time [80–82]. There is a growing trend toward using frameless systems with image-guided positioning

for radiosurgical applications, and several Image Guided Radiation Therapy techniques appear to offer excellent accuracy [83–85].

Cyber knife (Accuray, Inc., CA, USA) offers a frameless robotic system for image-guided radiosurgery. The system consists of a X-band, ultralight, computer-controlled 6-MV LINAC mounted on a highly maneuverable robotic manipulator arm which has 6 degrees of freedom [86]. High range of motion of the robotic arm allows utmost flexibility in selecting beam directions and non-isocentric, highly conformal treatments of large, irregularly shaped targets is possible without the use of multiple overlapping isocenters [87]. The system offers multimodality image fusion capability which improves target definition. Automatic segmentation, contouring and dose optimization processes are also improved. Real-time monitoring of patient position allows for correcting intrafraction motion during robotic treatment delivery. While Cyber knife offers the ability of treating both intracranial and extracranial targets, planning for simultaneous treatment of multiple lesions is also possible.

Very recently, Cyber knife M6 Series has been introduced with the option of performing MLC-based robotic radiosurgery, which features improved conformal shaping of beam apertures. This system has great potential for improving treatment outcomes and efficiency with reduction in monitor units and treatment time. The implementation of fractionated treatment schedules may be more practical with this high-end model.

Although radiosurgery using the LINACs have a shorter history, unique developments have made LINAC-based SRS popular throughout the world. Newer techniques and dose planning software have been introduced to improve conformity of dose planning and delivery. Improved capability of beam shaping and intensity modulation enhanced conformality and normal tissue sparing. Introduction of jaws, noncircular, mini and microleaf collimators has greatly contributed to improve treatment precision over the years. Recent advances combined with their favorable aspects of higher mechanical flexibility, capability to achieve improved dose homogeneity and economical considerations make LINAC-based systems excellent tools for SRS. In the context of GJT radiosurgery, there are fewer studies using the LINAC-based systems [41,48–50,53–55,60,63–66]. However, currently available data indicate safety and efficacy of LINAC-based SRS comparable

to that of Gamma knife radiosurgery. With the recent advances, treatment outcomes of LINAC-based SRS for GJT will probably be further refined in the near future.

Conclusion & future perspective

Taken together, critical studies assessing the growing body of data on GJT management and most recent series using the Gamma knife or LINAC-based systems for GJT radiosurgery report excellent local control rates in the order of 90–100% with negligible toxicity [21–24,30,56–67] (Table 1). While the dose range for GJT radiosurgery varies widely between 10 and 30 Gy for single-fraction treatments in the literature, most of the series typically using a median marginal dose around 15 Gy reported excellent outcomes (Table 1). Two recent Cyber knife series reported 100% local control with a median dose of 25 Gy delivered in five fractions [63,66].

Substantial technological advances in radiation oncology, compiling clinical experience with continuously increasing longer follow-up

durations, and excellent therapeutic outcomes achieved in terms of excellent local control with a favorable toxicity profile have contributed to enhanced utilization of SRS for GJT management in recent years. Adopted concept of minimally invasive modern neurosurgical approaches and aforementioned recent advances in radiosurgery have led to a paradigm shift. Many tumors allocated to surgery in the past are now more judiciously treated with SRS. However, it should also be noted that these two modalities are both invaluable members of the therapeutic armamentarium and may be used interchangeably or sequentially in the multidisciplinary management setting. Nevertheless, tremendous recent progress in SRS may not be neglected and it appears reasonable to consider SRS as the first-line noninvasive therapeutic option in majority of patients with GJT whilst realizing the merits of multidisciplinary management.

In the context of future perspectives, antian-tigenic agents are increasingly used together with radiation therapy to enhance the effect of

Table 1. Selected publications of radiosurgery for glomus tumors including the most recent series.

Study	Study year	Patients (n)	Radiosurgery modality	Dose (Gy)	Local control	Mean or median duration of follow-up	Ref.
Liscak <i>et al.</i>	1999	66	Gamma knife SRS	Median marginal dose 16.5 Gy (range: 10–30 Gy) delivered in a single session	100	Median 24 months (range: 3–70 months)	[35]
Saringer <i>et al.</i>	2001	13	Gamma knife SRS	Median marginal dose 12 Gy (range: 9–14 Gy) delivered in a single session	100	Mean 50.4 months (range: 8–80 months)	[37]
Foote <i>et al.</i>	2002	25	Gamma knife SRS	Median marginal dose 15 Gy (range: 12–18 Gy) delivered in a single session	100	Median 37 months (range: 11–118 months)	[38]
Maarouf <i>et al.</i>	2003	14	LINAC SRS	Median marginal dose 15 Gy (range: 11–20 Gy) delivered in a single session	100	Median 48 months (range: 9.6–108 months)	[41]
Genc <i>et al.</i>	2010	18	Gamma knife SRS	Median marginal dose 15 Gy (range: 13–20 Gy) delivered in a single session	94.4	Mean 52.7 months (range: 12–116 months)	[57]
Wegner <i>et al.</i>	2010	18	LINAC SRS	Median marginal dose 20 Gy (range: 16–25 Gy) delivered in 1–5 sessions	100	Median 22.5 months (range: 9–82 months)	[60]
Lee <i>et al.</i>	2011	14	Gamma knife SRS	Mean marginal dose 13.7 Gy (range: 12.5–15 Gy) delivered in a single session	100	Median 40.3 months (range: 13.2–143.7 months)	[61]
Liebersson <i>et al.</i>	2012	36	LINAC and Cyber knife SRS	Median marginal dose 20 Gy (range: 14–25 Gy) delivered in 1–5 sessions	100	Median 57.6 months (range: 1–193 months)	[22]
Sheehan <i>et al.</i>	2012	132	Gamma knife SRS	Median marginal dose 15 Gy (range: 10–18 Gy) delivered in a single session	93	Median 50.5 months (range: 5–220 months)	[62]
Hurmuz <i>et al.</i>	2013	14	Cyber knife SRS	25 Gy in 5 fractions	100	Median 39 months (range: 7–60 months)	[63]
de Andrade <i>et al.</i>	2013	15	LINAC SRS	Mean marginal dose 14 Gy (range: 12–20 Gy) delivered in 1–5 sessions	100	Mean 35.4 months (range: 3–61 months)	[64]
Sager <i>et al.</i>	2014	21	LINAC SRS	Median marginal dose 15 Gy (range: 10–20 Gy) delivered in a single session	100	Median 49 months (range: 3–98 months)	[65]
Chun <i>et al.</i>	2014	31	Cyber knife SRS	25 Gy in 5 fractions	100	Median 24 months (range: 4–78 months)	[66]

LINAC: Linear accelerator; SRS: Stereotactic radiosurgery.

treatment [88–91]. From this point of view, the use of SRS in combination with antiangiogenic agents may offer superior results and should be actively investigated.

Given the potential dosimetric advantages of protons in terms of enhanced conformality of radiation dose, the use of proton beam SRS for GJT may offer improved normal tissue sparing and warrants thorough investigation.

Although several studies have addressed the utility of fractionated stereotactic irradiation of GJT using LINAC-based systems [49,50,54,60,63,66], currently available experience may be enriched by adding data on the utility of fractionated stereotactic treatments using Gamma knife systems with relocatable noninvasive immobilization systems. This approach may enable the treatment of larger GJT whilst exploiting the high mechanical accuracy of Gamma knife radiosurgery [75,76].

The spectrum of radiosurgery has expanded to include extracranial targets. Although poorly addressed so far, treatment of glomus tumors in other extracranial body sites may potentially be achieved through the utilization of real-time Image Guided Radiation Therapy and gating technologies. Radiosurgery may offer a viable tool for the treatment of multifocal lesions.

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