

# Long-term Outcomes After Radiosurgery for Temporal Bone Paragangliomas

Stacey M. Scheick, MD,\* Christopher G. Morris, MS,\* Robert J. Amdur, MD,\*  
Frank J. Bova, PhD,† William A. Friedman, MD,† and William M. Mendenhall, MD†

**Objectives** To determine the long-term outcome after stereotactic radiosurgery (SRS) for temporal bone paragangliomas.

**Materials and Methods:** We retrospectively reviewed the medical records of 11 patients with temporal bone paragangliomas (10 patients with a glomus jugulare tumor and 1 patient with a glomus tympanicum tumor) treated between January 1997 and July 2012 at the University of Florida with SRS to a median dose of 15 Gy in 1 fraction. Ten previously unirradiated patients received SRS as did 1 patient who received prior fractionated radiotherapy (FRT) and then received salvage SRS for a local recurrence. The major outcome endpoint was local control, meaning no further growth or shrinkage on follow-up computed tomography or magnetic resonance imaging scans.

**Results:** The median follow-up time was 5.3 years. Two patients developed a local recurrence after SRS, including the patient who received salvage SRS after prior FRT. The overall local control rates at 5 and 10 years were both 81%. The cause-specific survival rates at 5 and 10 years were both 88%. The distant metastasis-free survival rates at 5 and 10 years were both 100%. The overall survival rates at 5 and 10 years were both 78%. There were no severe complications.

**Conclusions:** SRS for benign head and neck paragangliomas is a safe and efficacious treatment associated with minimal morbidity. SRS is suitable for patients with skull base tumors <3 cm when FRT is logistically unsuitable. Surgery is reserved for patients in good health whose risk of associated morbidity is low. Observation is a reasonable option for asymptomatic patients with a limited life expectancy.

**Key Words:** outcomes, head and neck, radiosurgery, chemodectoma, paraganglioma

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Paragangliomas are an uncommon neuroendocrine neoplasm that account for <1% of head and neck tumors.<sup>1</sup> They are benign in 90% to 95% of cases. Most are sporadic, but they may be familial in 7% to 9% of patients and, if so, are often multiple.<sup>2</sup> Paragangliomas within the head and neck arise mainly from 4 primary locations: the carotid body at the common carotid artery bifurcation (carotid body tumors), the jugular bulb (glomus jugulare), along the vagus nerve (glomus vagale), and within the middle ear along the tympanic (Jacobson's) or auricular (Arnold's) nerves (glomus

tympanicum). Presenting symptoms will differ depending on location. Only 2% to 5% of paragangliomas secrete catecholamines.<sup>3</sup>

Carotid body tumors are the most common, accounting for approximately 60% of paragangliomas,<sup>4</sup> and will typically present as a painless, mobile, slow-growing neck mass that may be pulsatile and transmit bruits. If these tumors extend into the parapharyngeal space, they can be associated with cranial nerve (CN) palsies (typically 10 and 12) and can damage the sympathetic chain through further progression.

Glomus jugulare tumors may be associated with bone destruction. Patients with these tumors can present with CN deficits, typically 9 through 12. These tumors can originate and spread along the tympanic canaliculus, invading superiorly into the middle ear and inferiorly toward the jugular fossa. Large glomus jugulare tumors can cause CN 7 and CN 8 deficits from mass effect.

Glomus vagale tumors can present as an intraoral parapharyngeal mass that anteriorly displaces the tonsil or as a painless insidious lateral neck mass behind the angle of the mandible. They can arise from any 3 of the vagal ganglia, but will usually originate from the largest and most caudal: the ganglion nodosum. Somewhat similar to glomus jugulare tumors, deficits in CN 10 through CN 12 can be seen as these tumors progress and Horner syndrome can develop.

Glomus tympanicum is likely to present with hearing loss, pulsatile tinnitus, and disequilibrium, and on physical examination may appear as a reddish mass behind the eardrum. Unlike the glomus jugulare, ossicular chain destruction is unusual,<sup>5</sup> but they may spread to the mastoid air cells, eustachian tube, and nasopharynx.<sup>6</sup>

Clinically, paragangliomas are stratified into benign and malignant neoplasms. Malignancy is defined by clinical behavior, the development of metastases, and not on histologic appearance. Less than 10% of paragangliomas are malignant.<sup>7</sup>

Typically, paragangliomas demonstrate a median growth rate of 1.0 mm/year with a median tumor doubling time of 4 years.<sup>8</sup> However, a subset of patients will present with CN deficits. Death from paraganglioma is very rare, and treatment of these tumors is aimed at minimizing morbidity rather than improving survival.

Treatment is controversial and options include surgery, radiotherapy (RT), and stereotactic radiosurgery (SRS). Patients who are elderly and infirm with a limited life expectancy may be observed. The optimal treatment approach depends on the location and extent of the paraganglioma(s) as well as the medical comorbidities of the patient. Resection of skull base paragangliomas often requires sacrifice of 1 or more CNs and may result in significant permanent morbidity. Fractionated external-beam radiotherapy (FRT) is a safe and effective treatment but requires a 5-week treatment course, which may be logistically unattractive. SRS is an attractive alternative because an operation is unnecessary and a single,

From the Departments of \*Radiation Oncology; and †Neurosurgery, University of Florida College of Medicine, Gainesville, FL.

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Reprints: William M. Mendenhall, MD, Department of Neurosurgery, University of Florida College of Medicine, 2000 SW Archer Rd, P.O. Box 100385, Gainesville, FL 32610-0385. E-mail: mendwm@shands.ufl.edu.

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tightly focused dose of irradiation may be administered in 1 fraction. There are limited long-term data reporting the long-term outcomes of SRS relative to surgery or RT. The main purpose of this study was to determine the long-term local control rates for temporal bone paragangliomas after SRS.

## MATERIALS AND METHODS

Between 1997 and 2012, 10 patients with a glomus jugulare tumor and 1 patient with a glomus tympanicum tumor were treated with SRS at the University of Florida. These patients represent a minority of patients treated with irradiation during that time period. For perspective, Gilbo et al<sup>9</sup> reported on 131 patients treated with FRT between 1968 and 2011. Ten patients had benign paragangliomas and 1 patient was classified as having a malignant tumor. The latter patient had a glomus jugulare and was initially treated as a benign paraganglioma with postoperative FRT after a subtotal resection (STR). He recurred locally 6.1 years later and SRS was given as salvage therapy for the recurrence of the apparently benign paraganglioma. However, the tumor then recurred locally and in the neck 3.3 years later and was classified as malignant. The patients' medical records were reviewed under an institutional review board–approved protocol. Patients were presented at weekly head and neck tumor boards. FRT was recommended either because the risk of surgery-associated morbidity was considered to be too high or, less commonly, because residual tumor remained following a surgical resection. SRS was recommended for tumors that were <3 cm because of either patient preference or inability to undergo a 5-week course of FRT. All of the patients in this study were treated with SRS. All patients had pretreatment computed tomography (CT) or magnetic resonance imaging (MRI) scans. The gross tumor volume was defined on the planning CT fused with the treatment planning MRI. The planning target volume was the same as the gross tumor volume so that no margin of normal tissue was included in the planning target volume. A linear accelerator-based system was used and a sphere-packing technique was used to achieve the optimal dose distribution. The median total dose of radiation delivered was 15 Gy in 1 fraction (range, 12.5 to 15 Gy). All patients were treated with a single fraction. Patient characteristics are depicted in Table 1.

Severe complications were defined as those that necessitated hospitalization, surgical intervention, or resulted in death. Other complications coded as severe included a new or worsening CN deficit, disequilibrium, and development of an RT-induced malignancy.

For follow-up, patients were typically seen annually with a physical examination and CT or MRI to assess tumor response to RT. We defined local control as stable disease or partial regression. Local recurrence was defined as increased tumor size. Conversely, local control was defined as lack of progression. Locoregional control was defined as control of disease at the primary site and in the neck.

Follow-up was calculated from the date of SRS. All patients had a 2-year minimum follow-up. One patient was lost to follow-up at 5.3 years after treatment and had no evidence of disease progression at that time. Median follow-up on all patients was 5.3 years (range, 2.7 to 16.6 y). Median follow-up on survivors was 11.2 years (range, 2.7 to 16.6 y).

SAS and JMP software were used for statistical analysis (SAS Institute, Cary, NC). The Kaplan-Meier product-limit method provided estimates of local control, freedom from distant metastasis, overall survival, and cause-specific survival. Cause-specific survival was defined as death due to disease or

**TABLE 1. Patient Characteristics (11 Patients)**

Characteristics	Patients [n (%)]
Sex	
Men	9 (81)
Women	2 (19)
Age (median [range]) (y)	50 (30-88)
Race	
White	7 (64)
Black	3 (27)
Other	1 (9)
Tumor location: side of the neck	
Left	6 (55)
Right	5 (45)
Prior treatment	
None	7 (64)
FRT only	0
Surgery only	1 (9)
Biopsy only	2 (18)
Surgery and FRT	1 (9)
CN deficits	8 (73)
CN 6	1 (9)
CN 7	1 (9)
CN 8	7 (64)
CN 9-10	3 (27)
CN 11	1 (9)
CN 12	1 (9)
Median follow-up (range) (y)	
All patients	5.3 (2.7-16.6)
Living patients	11.2 (2.7-16.6)

CN indicates cranial nerve; FRT, fractionated radiotherapy.

complications. Death in the presence of uncontrolled paraganglioma was also defined as death due to disease, as was the case of the patient who died due to disseminated melanoma.

## RESULTS

One patient with a glomus jugulare recurred locally 7 months after SRS. This patient received salvage RT for what was deemed to be a marginal miss, and has been locally controlled since that time. One patient was initially treated as a benign paraganglioma with postoperative FRT after a STR. The patient locally recurred 6.1 years later and received SRS as salvage therapy for the recurrence of an apparently benign paraganglioma. The patient later recurred locally and in the neck 3.3 years after SRS and was classified as having a malignant tumor. The patient subsequently died of metastatic melanoma before a second salvage procedure could be performed. The overall local control rates at 5 and 10 years were both 81% (Fig. 1).

The cause-specific survival rates at 5 and 10 years were both 88%; the freedom from distant metastases rates at 5 and 10 years were both 100%; and the overall survival rates at 5 and 10 years were both 78% (Fig. 2).

Two of the 11 patients experienced 1 or more relatively modest complications; one reported worsening hearing loss and the other reported new-onset disequilibrium after SRS. There was nothing about the presentation or treatment of these 2 patients that would have predicted an increased risk of toxicity compared with the remaining 9 patients.

Eight of the 11 patients (73%) had pretreatment CN deficits, all of whom had glomus jugulare tumors. Four of the 8 patients underwent surgery (biopsies only, 2; STR, 1; and unknown extent of resection, 1 patient), and none of the

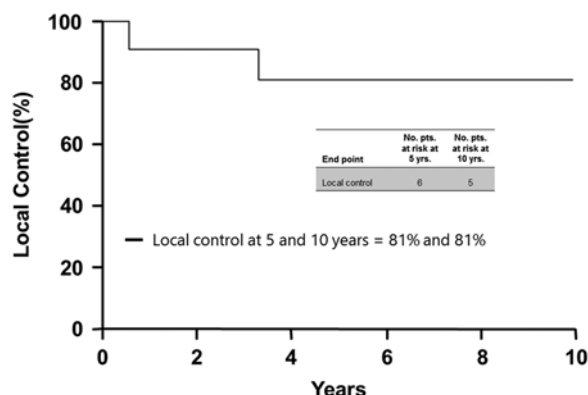


FIGURE 1. Local control rates at 5 and 10 years.

mentioned patients had new deficits or worsening deficits after surgery. The most common CN deficit was CN 8, which affected 63% of all patients. The next most common deficit was CN 9-10, which affected 27% of all patients. Table 1 lists all CN deficits reported. Of those with pretreatment deficits, only 1 patient reported worsening hearing loss after SRS, 1 patient reported improved hearing and a completely resolved CN 6 palsy after SRS, and 6 patients reported no change in their pretreatment symptoms after SRS.

No patient developed a severe complication or radiation-induced malignancy.

## DISCUSSION

The treatment options for patients with head and neck paragangliomas include surgery, FRT, SRS, and observation. Traditionally, surgery has been the preferred treatment, with the goal being complete resection. However, total resection often involves significant comorbidities, given the tumor's vascularity and the associated surrounding critical structures. FRT has been used as primary treatment for patients who are not surgical candidates due to the anticipated morbidity of resection, medical comorbidities, incompletely resectable disease, or postoperative residual disease; it is used as salvage therapy for failures after surgery. Unlike surgery, for which the goal is complete resection, the goal of radiation treatment is to stop further growth and promote possible tumor shrinkage over time. For surgical cases, local control refers to the lack of recurrence after a gross total resection. Parenthetically, STR is to be discouraged. It increases morbidity and does nothing to reduce the morbidity or improve the likelihood of local control after irradiation.

A recent systematic literature review by Suarez et al<sup>10</sup> of 2042 patients with glomus jugulare and glomus vagale tumors treated with surgery, FRT, and SRS showed that the likelihood of local control was better after FRT ( $P=0.002$ ) and that the probability of a major complication was lower ( $P=0.003$ ) compared with surgery. Jacob et al<sup>11</sup> reported on 57 patients treated with SRS at the Mayo Clinic between 1990 and 2007; the mean tumor dose to the margin was 15.3 Gy. Imaging follow-up was available for 54 patients at a mean of 48 months. Fifty-three patients either had a regression or stable disease; 1 patient progressed 99 months after SRS; the local control rates were 100% at 7 years and 83% at 10 years. A review of the literature regarding temporal bone paragangliomas shows that local control rates for surgery have improved with newer surgical techniques, but they typically do

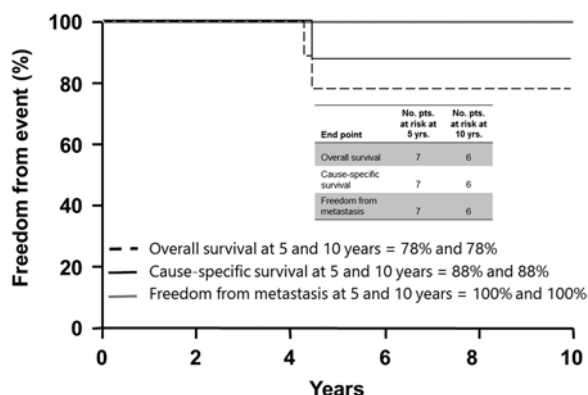


FIGURE 2. Overall survival, cause-specific survival, freedom from metastasis, locoregional control, local control, and neck control rates at 5 and 10 years including the number of patients at risk.

not exceed the local control rates seen with FRT. Further, complications continue to exceed those seen after FRT.

CN palsies are also more common after surgery than after FRT. Suarez et al<sup>10</sup> found that the probability of CN palsies was 181.6% higher in comparison with preoperative levels for surgical candidates, whereas for SRS and FRT the probability of CN palsies decreased to 8.8% and 4.1%, respectively. Jacob et al<sup>11</sup> noted that hearing loss developed in 54% of patients after SRS. In our study, 73% patients had pretreatment CN palsies, and no patient developed a new CN palsy after SRS.

The greatest advantage of SRS over FRT is patient convenience. When comparing FRT and SRS, Suarez et al<sup>10</sup> found no difference in the local control rates; however, the median follow-up times for FRT and SRS in that series were 9.38 and 3.43 years, respectively. A prior study at our institution of 131 patients with paragangliomas treated with FRT to a median dose of 45 Gy showed control rates of 99% and 96% at 5 and 10 years, respectively.<sup>9</sup> Control rates after FRT range from 89% to 99% at 5 years and from 90% to 96% at 10 years.<sup>9,10,12,13</sup> Control rates after SRS range from 89% to 100% at 5 years.<sup>3,10,14-16</sup> In this study, the control rates after SRS were 81% at both 5 and 10 years. The local control rates in our study appear to be consistent with those reported in the literature. Our study has the longest median follow-up in the literature thus far. Although it is disappointing to see a local control rate that is somewhat lower than what we have observed after FRT at our institution, our study is limited by a much smaller sample size, and further long-term data with larger patient samples are needed. In addition, 1 of 11 patients had been previously irradiated and received SRS as salvage for a local recurrence. Thus, 9 of 10 previously unirradiated patients treated with SRS were locally controlled.

It is also important to consider the known risk of radiation-induced malignancy. Lalwani et al<sup>17</sup> estimates the rate of radiation-induced sarcoma to be 3% to 5% at an average of 8 to 10 years, and points out that, although this risk is low, the development of this complication is often lethal, as opposed to most surgical complications. This is likely to be a gross overestimate and, in fact, Gilbo et al<sup>9</sup> reported no radiation-induced malignancies in 131 patients treated with FRT at our institution. Many of these patients were followed for 10 to 15 years or longer. The probability of a radiation-induced malignancy after FRT is likely to be about 1 in 500 with a latency period of 7 to 10 years or longer. To date, no case of a radiation-induced malignancy after SRS has been reported, and

Sheehan et al<sup>16</sup> postulate that the risk of RT-induced malignancy is negligible with SRS.

Observation is also an option for patients who are asymptomatic and have a limited life expectancy. However, appropriate counseling should include the risk of CN deficits and other complications as the tumor progresses.

## CONCLUSIONS

SRS for benign head and neck paragangliomas of the temporal bone is a safe and efficacious treatment associated with minimal morbidity. It is suitable for patients with skull base tumors <3 cm where FRT is logistically unsuitable. Surgery is reserved for patients in good health whose risk of associated morbidity is low. Observation is a reasonable option for asymptomatic patients with a limited life expectancy.

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