The long-term outcome of CyberKnife therapy for head and neck paraganglioma: Management suggestion from a single center experience

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Abstract

To analyze the long-term follow-up data of CyberKnife treatment (CKT) for head and neck paragangliomas (HNPGs). Patients who received CKT to HNPGs from 2010 to 2019 were retrospectively reviewed. A total of 34 HNPGs from 29 patients were identified. The mean age was 50 (± 16) years old, and 15 patients (52%) were female. Previous operation was done in 15 patients (55%). Four cases (14%) were functional in hormone production. According to Fisch classification, one case (3%) was B, 12 (42%) were C, 14 (48%) were D, and two cases (7%) were out of classification. The median prescribed dose covered 95% of the planning target volume was 2500 (IQR 2100–2600) cGy and the median target volume was 10 (IQR 5.8–21.3) cm^3. The local control rate was 97%. The median progression-free survival was 66 (IQR 28–95) months and 96% were free of tumor progression at eight years. During the follow-up, one case (3%) resulted in permanent facial nerve palsy (House-Brackmann grade II), and another case (3%) resulted in asymptomatic cerebellar radiation necrosis. Univariate and multivariate analysis showed no previous surgical history (OR 8.58, 95% CI 1.2–59.7, p = 0.03) was a positive predictor of symptom improvement. We devised a treatment flow-chart based on our finding. CKT for HNPGs was an effective treatment with little side effect over the long term and may have a role in the first-line therapy especially for symptomatic nonfunctional HNPGs for better symptom control.

Introduction

Paragangliomas, also known as glomus tumors, in the head and neck may be difficult to treat.[5, 19] They are WHO grade I tumor, and commonly arise in the jugulotympanic regions[13], making it difficult to perform complete surgical excision with leaving the surrounding nerves and vessels intact.[3] A strong tumor enhancement on computed tomography and magnetic resonance image (MRI) helps make the diagnosis and hypervascularity on digital subtraction angiography confirms the diagnosis in difficult cases.[16, 6] Due to their origin in neural crest cells associated with autonomic ganglia, the jugulotympanic paragangliomas may secrete catecholamine, in which case they are called functional paragangliomas.[13] Most skull base paragangliomas are treated by surgical resection, endovascular embolization, radiation, and their combination. The two main kinds of stereotactic radiosurgery or radiotherapy are gamma knife, and CyberKnife. Compared to gamma knife, CyberKnife outcome has not been published as much.[2, 1] To further accumulate long-term evidence of CyberKnife therapy (CKT) on head and neck paragangliomas (HNPGs), we analyzed the outcome of cases from our center. Since no treatment guidelines for HNPGs exist[1], we aimed to establish our own management flow-chart if we found anything meaningful from the analysis.

Methods

We defined the HNPGs as either carotid body paragangliomas or jugulotympanic paragangliomas. Patients who received CKT for HNPGs in the period from 2010 to 2019 were included and various data were recorded including age, sex, signs and symptoms before CKT, side of radiation, history of previous operation or radiation, functionality in hormone production by the tumor, the number of tumors, Fisch

classification[4], form of treatment (primary, adjuvant, or secondary for relapsed cases), parameters for CKT, radiological response, changes in symptoms, adverse radiation effect (ARE), and the length of follow-up among others. The diagnosis of HNPGs was made radiologically by MRI with or without DSA for non-operated patients, and further confirmed pathologically for operated patients. 6D-skull tracking algorithm was used. The applied radiation dose were the same between the functional and non-functional paragangliomas. Based on the MRI, we defined the response to CKT into three categories of partial response (PR), sustained disease (SD), and progressive disease (PD) using the largest diameter as a reference. ARE was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) if listed. From the acquired data, univariate and multivariate analyses were performed to identify prognostic factors for tumor progression and symptoms improvement. The factors whose p value less than 0.1 from the univariate analysis were considered for multivariate analysis. Multicollinearity test was done to identify factors to exclude in multivariate analysis. Progression-free survival (PFS) and overall survival (OS) curves were drawn.

Surgical resection was indicated for all the functional HNPGs, and as for non-functional ones, surgery was considered if one of the following criteria was met: 1) 95% or more resection was feasible, 2) mass reduction was necessary for subsequent CKT because of large tumor volume, 3) immediate decompression was felt to be needed for cranial neuropathy, or 4) definitive tissue diagnosis was needed for equivocal cases. Postoperatively, adjuvant CKT was recommended to those with residual tumor.

Statistical analysis was done using SPSS version 25.0 (IBM Inc., Armonk, NY, USA). The values were listed as means for parametric data, and median for nonparametric data. Shapiro-Wilk test was used to tell parametric from nonparametric data. Binary logistic regression was used to evaluate the prognostic factors for radiological outcome and symptom improvement. Kaplan-Meier method was used to draw PFS and OS curves from the last day of CKT. P value of 0.05 or less was considered statistically significant.

Our institutional review board did not require informed consent for study participation because this study relied on information obtained as part of routine clinical practice.

Results

A total of 29 patients and 34 tumors were identified (Table 1). Female constituted 52% of the patients. The common symptoms were hearing impairment (52%), tinnitus (52%), hoarseness (42%), and dysphagia (34%). Out of the 15 cases of hearing impairment, four were Gardner-Robertson scale (GR) 1, five were GR 2, two were GR 3, two were GR 5, and the two were unknown (not described in the medical chart). As for the six cases of facial palsy (21%), two were House-Brackmann grade (HB) I, one was HB II, one was HB III, and the other two were HB IV. Previous operation were performed in 15 cases (52%). Among them, 95% or more resections were performed for seven cases. Four operations were done for functional HNPGs. Two were for mass reduction for subsequent CKT. One for immediate abducens nerve decompression for tumor mass effect. And one for open biopsy due to equivocal case. Two patients (7%)

had previous history of radiation treatment. One had radiotherapy by linear accelerator knife (24Gy in four fractions) about 12 years before, and the other one had external beam radiation therapy (unknown dose in 23 fractions) about 4.5 years ago. Four cases (14%) were functional in catecholamine production by HNPGs, and all underwent surgical resection before CKT. Most of the tumors were Fish classification[4] D1 or D2 (14 cases, 48%) at the time of CKT. Two cases were not classified according to Fisch classification, as they were neither glomus jugulare or tympanicum. The most common form of CKT was primary treatment (14 cases, 48%), followed by treatment for relapsed tumors (12 cases, 42%) and adjuvant treatment (3 cases, 10%). The median time between the previous surgery and CKT was 25 months and that for relapsed tumors was about 40 months (Table 1). The parameters of CKT is summarized in the Table 2. All therapy were done in multisession and the median target tumor volume was 10 (5.8–21.3) cc. Two patients had more than one tumors, of which only the one symptomatic tumor were treated and the other asymptomatic ones were observed. The asymptomatic ones in the two patients remained the same in size for 31 and 61 months respectively until one of them was treated with CKT as per the patient's strong wish.

Table 1
Summary of the baseline patient characteristics

Total	**29**
Age (mean) (yr)	50 ± 16
Female	15 (52%)
Symptoms	6 (21%)
Facial palsy	3 (10%)
Occasional facial spasm	2 (7%)
Dysgeusia	15 (52%)
Hearing impairment	15 (52%)
Tinnitus	4 (14%)
Dizziness	12 (42%)
Hoarseness	10 (34%)
Dysphagia	2 (7%)
Dysarthria	
Right side of radiation	16 (55%)
Previous operation	15 (52%)
Previous radiation	2 (7%)
Hormonally functional	4 (14%)
Multiple lesions in the head and neck	2 (7%)
Fisch classification	1 (3%)
B	12 (42%)
C	14 (48%)
D	2 (7%)
Others	
Form of CKT	14 (48%)
Primary Tx	3 (10%)
Adjuvant Tx	12 (42%)
Tx for relapsed tumor	

Total	29
Time from the last surgery to relapse (mos) (median) (IQR)	37.0 (8.0–72.5)
Time from the surgery to CKT (mos) (median) (IQR)	25 (8–56)
Adjuvant Tx (mos) (median) (IQR)	4 (3.5–8.0)
Tx for relapsed tumor (mos) (median) (IQR)	40.5 (10.0–83.0)

Table 2
Summary of CyberKnife therapy

D95 (median) (IQR) (cGy)	2500 (2100–2600)
Fraction (median) (IQR)	5 (3–5)
Target (tumor) volume (median) (IQR) (cm^3)	10 (5.8–21.3)

The outcome of CKT is summarized in the Table 3. Local control (PR + SD) was achieved in 97%. The median time to confirm radiological PR was 12 (IQR 6–17) months. One PD case (3%) deteriorated due to metastasis to a thoracic vertebral body 17 months following the last CKT, which required an emergent surgery. He had a mass reduction surgery for his carotid body paraganglioma, which was found because of neck mass and lower cranial neuropathies. Four months after the operation, CKT was applied for a prescribed dose covering 95% of the planning target volume (D95) of 3000cGy in 10 fractions for target tumor volume of 171cc. The image at the time of PD was not available as he was treated in the other medical facility. He committed suicide 59 months after the last CKT. The death was not directly due to the tumor. As for the symptom control, 45% of patients had some improvement. The most likely symptom to improve was tinnitus (53%) over the mean time of 28 (± 11) months from the CKT. The other improved symptoms and their duration are summarized in the Table 3. As for the hearing impairment, although five patients (33%) improved, all improvement was within the same GR scale. Although all of them experienced subjective improvement in their hearing deficits, we evaluated objectively in only two patients by pure tone average (one patient improved from 40 to 32.5dB, and another one improved from 23.8 to 12.5dB). On the other hand, no one had any subjective improvement in facial palsy, dysgeusia, or dysarthria. As for the ARE, one case (3%) resulted in asymptomatic radiation necrosis in the cerebellar hemisphere near the radiated region (CTCAE grade 1), and another one (3%) resulted in facial nerve disorder (HB II, CTCAE grade 1). The one who had radiation necrosis had had no history of previous radiation treatment. Although ARE occurred in two cases (7%), only one (3%) of them (facial nerve disorder) was clinically significant. It occurred in a 28-year-old male patient with Fisch class B tumor. The D95 was 2100cGy in 3 fraction for 0.7cc target tumor volume. For the four functional HNPGs, where CKT was performed for relapses, serum level of norepinephrine (S_{NE}) was the main laboratory marker to check as well as MRI. Before CKT, the mean level of S_{NE} was 1000 (± 267) pg/ml (normal range: 100–450 pg/ml). After CKT, the mean S_{NE} was 476 pg/ml and under control (post-CKT S_{NE} were unavailable in two

cases, whose follow-up were made in the other facilities). The S_{NE} level started to decrease two to three months after CKT.

Table 3
Outcome after CyberKnife therapy (CKT). Value written in italic were parametric data and represented in the mean value (± standard deviation), whereas nonparametric data were represented in the median value (interquartile range).

Radiological outcome	**n (%)**	**The time from the last CKT (months)**
PR	**17 (59%)**	**12 (6–17)**
SD	**11 (38%)**	**-**
PD	**1 (3%)**	**17**
The number of patients whose symptoms improved	13 (45%)	*25 (± 15)* for PR + SD *27 (± 17)* for PR
Occasional facial spasm	1 (33%)	29
Hearing impairment	5 (33%)	*23 (± 11)*
Tinnitus	8 (53%)	*27.5 (± 10.7)*
Dizziness	2 (50%)	*37.5 (± 31.8)*
Hoarseness	4 (33%)	*30.7 (± 23.0)*
Dysphagia	1 (10%)	5
Adverse radiation effect	1 (3%)	85*
Facial nerve disorder*	1 (3%)	40
Asymptomatic cerebellar necrosis**	1 (3%)	59
Dead***		
PFS	-	66.0 (28.0–95.0)
OS	-	66.0 (28.5–95.0)
*House-Brackmann grade II (CTCAE grade 1), which was diagnosed when he presented for a follow-up for the first time in eight years after. It was unclear when he developed the facial palsy.		
**Small radiation necrosis in the right cerebellar hemisphere near the radiated region		
***Due to suicide		

The medians of radiological (PFS) and clinical follow-up period (OS) were both 66 months. PFS and OS curves were drawn in the Fig. 1. PFS at 3, 5, and 7 years were 94.1%, 93.8%, and 91.7% respectively. We illustrate two PR cases as examples (Fig. 2).

Analysis for prognostic factors

Univariate analysis for the symptoms improvement showed that age, and having no history of previous surgery were statistically significant factors for recovery of symptoms (Table 4). Age, sex and the status of having no previous operation (p < = 0.1) were included in the multivariate analysis, the result of which is summarized in the Table 4. The status of no history of surgery remained still significant (p = 0.03). The same kind of analysis was performed exclusively in the nonfunctional group (no hormone production by the tumor). The two factors (female sex, and no history of previous operation) were significant (p = 0.05) for symptom improvement. Univariate analysis for the PD (local control failure) resulted in no variables (age, sex, previous operation, time to CKT, target volume, and firm of CKT) to be statistically significant (not shown).

Table 4
Univariate and multivariate analyses on the improvement of overall symptoms.

	Overall improvement		**Overall improvement (nonfunctional group)**	
	Univariate (p value)	Multivariate (OR, 95% CI, p value)	Univariate (p value)	Multivariate (OR, 95% CI, p value)
Age	**0.05**	1.06, 1.0–1.1, 0.07	0.12	
Sex (female)	**0.10**	2.61, 0.4–16.7, 0.31	**0.03**	6.7, 0.9–47.3, **0.05**
Side of CKT	0.11		0.32	
No previous operation	**0.02**	8.58, 1.2–59.7, **0.03**	**0.03**	6.7, 0.9–47.3, **0.05**
Previous radiation	0.88		0.95	
Functional	0.41		-	
Fisch classification	0.32		0.33	
Form of CKT	0.14		0.20	
Time to CKT	0.82		0.76	
Target tumor volume	0.77		0.98	
Radiological outcome	0.81		0.46	

Discussion

In this study, we confirmed the long-term effectiveness of CKT to the HNPGs with acceptable rate of clinically significant adverse effects (3%). We also found that those patients with no history of surgical excision of their HNPGs were more likely to have improvement in symptoms after CKT (Table 4). Although quite a few case series demonstrating the effects of gamma knife treatment to HNPGs exist[14, 20, 8, 19], CKT evidence for these tumors still need to be accumulated especially long-term results[1]. We believe that our series of 29 cases, although the number of cases are not as many as some previous studies, the relatively longer median follow-up period of 66 months (15 cases were followed for more than five years) adds further valuable data to the current literature.

Radiological tumor control

In the median follow-up of 66 months, 97% (28/29) local control rate was attained and we observed one (3%) PD at 17 months from the last CKT. The interquartile range PR was observed was six to 17 months from the last CKT (Table 3). Based on this, radiological outcome after CKT may be more likely to be determined within the first two years. One thing should be mentioned to the PD case is that systemic screening for HNPGs metastasis was not done before CKT and that we are not sure that the case was in-field or out-field recurrence. Considering the fact that about 5% of HNPGs are associated with malignancy[5, 7], systemic screening should have been done at some time around the CKT. No prognostic factors for PD were identified in our series as was the case with a similar past study.[17] This may be due to the small number of local control failure. The local control rate and the rate of ARE were in line with previous studies.[17, 1, 11] Our study adds to the evidence that CKT is effective to HNPGs. Although quite a few literature state the efficacy of radiation treatment to HNPGs, we do not have consensus guidelines for the treatment of HNPGs.[1] Several papers advocates the primary role of radiation treatment.[11, 18] However, all of these studies are retrospective ones, and we may need to have a randomized control trial comparing surgical resection with radiation treatment.

Symptom improvement and adverse effects

In our cohort, 45% (13/29) experienced some degree of symptoms improvement. It took more time for symptoms to improve (27 ± 17 months) than for tumors to decrease in size radiologically (12 (6–17) months) (Table 3). The symptom improvement rate after CKT in our study was within the reported range from the past studies (42–56%).[12, 19, 3, 17, 1] Tinnitus, dizziness, facial spasm, hearing impairment, hoarseness were more likely to improve than other symptoms (Table 3) and the fact that tinnitus and hearing impairment tend to improve was supported by a recent meta-analysis.[3] Univariate and multivariate analysis revealed that the status of no past surgical resection was a significant prognostic factor for better clinical outcome (Table 4). When subgroup analyses was performed for nonfunctional group, the female sex and no history of surgery were the two factors that showed significance to have a better symptom control. This is probably that, by the surgical impact, the nerves are more damaged than relieved by surgical resection. It is unclear why the female sex was more likely to respond clinically to CKT. It must be noted that, since not all the symptoms were objectively, or quantitatively evaluated pre-/

post- CKT, it is likely that some symptoms' improvement were susceptible to subjective feelings at the time of the follow-up. Nevertheless, it is the patients' satisfaction that counts in the real world, and even if the symptoms improvement was largely due to subjective feeling, the results are still applicable to the clinical practice to some extent. It should be mentioned that these findings were not previously endorsed by any other studies and that this finding remains to be carefully evaluated in the future studies. However, some meta-analyses[18, 9] found that cranial nerve deficits were higher in the gross total resection group than radiation treatment group. This finding indirectly supports our result that having no surgical history is a positive factor for symptom improvement. On the whole, to the best of our knowledge, no factors are consistently found to be a significant prognostic factor. One study showed that the female sex, right-sided tumor, primary radiation treatment, and hearing impairment symptoms to be negative prognostic factors for local control failure.[3] Another study found no significant prognostic factors for symptom improvement.[1] Other study showed that having a cranial neuropathy before radiation treatment was a risk factor for lack of symptom improvement.[17]

As for ARE, the rate was 7% (2/29), which is comparable to a previous similar study.[17] One was asymptomatic cerebellar radiation necrosis, the other one was facial nerve disorder (HB II). This facial palsy may be due to damage to the tympanic segment of the facial nerve. A recent meta-analysis revealed that CyberKnife was associated with the least likeliness of ARE compared to linear accelerator or gamma knife.[3] We compared our CKT results on HNPGs with other forms of treatment (Table 5). Overall, surgical resection alone seems to provide less local control rate than radiation therapy ± surgical resection despite higher risk of CN deficits.

Table 5
Comparison of our study's treatment outcome with some past literatures on other forms of treatment modality.

	Treatment modality	N of tumors	f/u period	Local control rate	Clinical AE
Jackson et al., 2001	Surgical resection only	182	54 mos mean	85%	New CN deficits (59%)
Almefty et al., 2002	Surgical resection only	28	38 mos mean	93%	New CN deficits (40%)
Fayad et al., 2010	Surgical resection only	47	26 mos mean	66%	Facial palsy (6.5%), Dysphagia (27%), dysarthria (27%)
Sallabanda et al., 2018 [1]	LINAC (90%), CK (10%) ± surgical resection	31	55 mos mean	97%	Transient early toxicities (13%)
Wong et al., 2014	EBRT (87%), SRS (13%) ± surgical resection	16	48 mos mean	94%	Xerostomia/ taste dysfunction (7%)
Liscak et al., 2014	GK ± surgical resection	45	118 mos median	98%	Tinnitus (2%)
Sheehan et al., 2012	GK ± surgical resection	134	50 mos median, 62 mos mean	93%	Worsening CN function despite radiological control (11%)
Our study	CK ± surgical resection	29	66 mos median, 63 mos mean	97%	Facial palsy (3%)

Management suggestion based on our series

Based on our series, and its outcome described above, we made a flow-chart for HNPGs management (Fig. 3). Once paraganglioma is in the differential diagnosis and radiologically likely, determination should be made whether it is symptomatic or not. If asymptomatic, it may be waited and scanned for follow-up. In a study, 45% of tumors remained stable or regressed in size over more than five years follow-

up.[15] On the other hand, treatment intervention should be considered for symptomatic ones based on its functionality. Since all four (14%) of our functional HNPGs were treated by surgical resection and observed to find their recurrence at the mean follow-up of 16 ± 15 months, we suggest surgical resection of the symptomatic functional HNPGs followed by CKT. We think the postoperative CKT may be performed only after the diagnosis of recurrence (or relapse), or as adjuvant therapy. Surgical option should be reserved for rapidly growing and functional tumors.[10, 1] Lieberson et al. suggested a treatment algorism, which had something in common with ours.[10] As for the symptomatic nonfunctional HNPGs, we think CKT is the best primary treatment based on the analysis in the Table 4 for better clinical symptom control. It may be treated primarily by surgical resection followed by CKT soon after the surgery as adjuvant therapy or at the time of radiological relapse as secondary therapy. In either way, since no prognostic factors for PD were found in our series as well as past studies, radiological control would not be affected. After CKT, the first two years should be closely monitored radiologically (Table 3) and S_{NE} level should be checked periodically if functional. Radiological improvement if any proceeds clinical improvement, which occurs even for SD population (Table 3). Also systemic screening for metastasis of HNPGs is strongly considered if not already done. As for concurrently found multiple HNPGs, each lesion can be managed in the same manner as our proposed flowchart. In our series, two patients (4%) had more than one HNPG. We performed CKT for only one symptomatic lesion in both patients and followed the other non-radiated lesions, which did not grow for 31 and 61 months respectively for two patients. One of them strongly wished to have the remaining non-growing lesions to be treated, and we did CKT for these legions in the end.

Limitations

The limitations were retrospective nature and that this study was carried out in single institution. Since our institution was a referred center for CKT, not all the detailed clinical and radiological information was available. And there was not enough number of PD cases to detect prognostic factors if any.

Conclusions

CKT is a safe, valid modality for HNPGs over the long term and may have a role even in the first-line therapy over surgery. We suggested management algorisms based on our case series' data and recommend primary treatment with CKT for symptomatic nonfunctional HNPGs.

Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: Not applicable.

Availability of data and material: Data transparency was confirmed.

Code availability: Not applicable

Ethical approval: This study was done under our institutional review board approval and did not require patient consent.

Consent to participate: Our institutional review board did not require informed consent for study participation because this study relied on information obtained as part of routine clinical practice.

Consent for publication: Our institutional review board did not require informed consent for study publication because the publication data were de-identified as for the information obtained.

Authors' contributions: All authors read and approved the final manuscript. SH made a study design, collected patient data, drafted and revised the manuscript. KK made a contribution to revising the original draft. KS, and SI were the supervisors.

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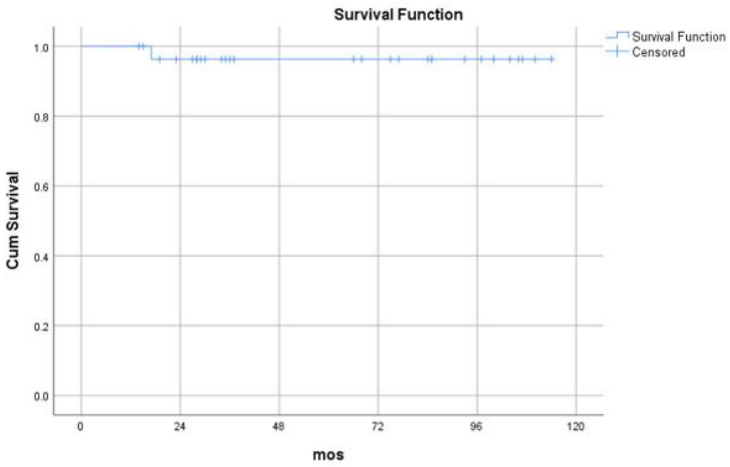
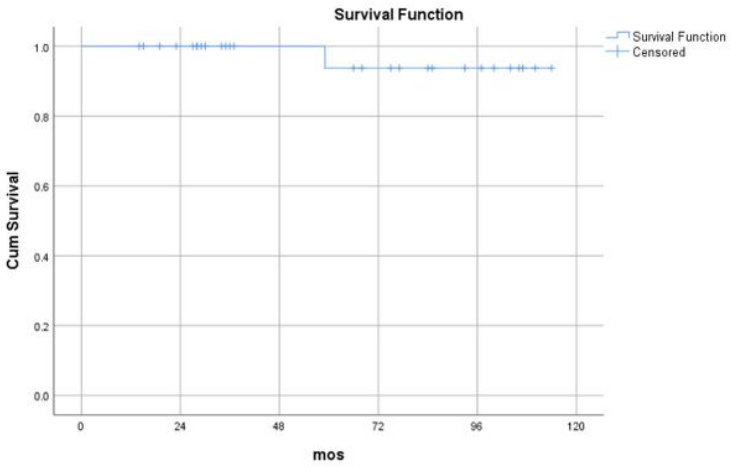
Figures



Year	0	2	4	6	8
PFS (%)	-	96	96	96	96
Number at risk (progression, cumulative)	29 (0)	25 (1)	16 (1)	14 (1)	8 (1)



Year	0	2	4	6	8
OS (%)	-	100	100	94	94
Number at risk (dead, cumulative)	29 (0)	25 (0)	16 (0)	14 (1)	8 (1)

Figure 1

Progression-free survival (left) and overall survival (right) of our study cohort in the median follow-up period of 66 months.

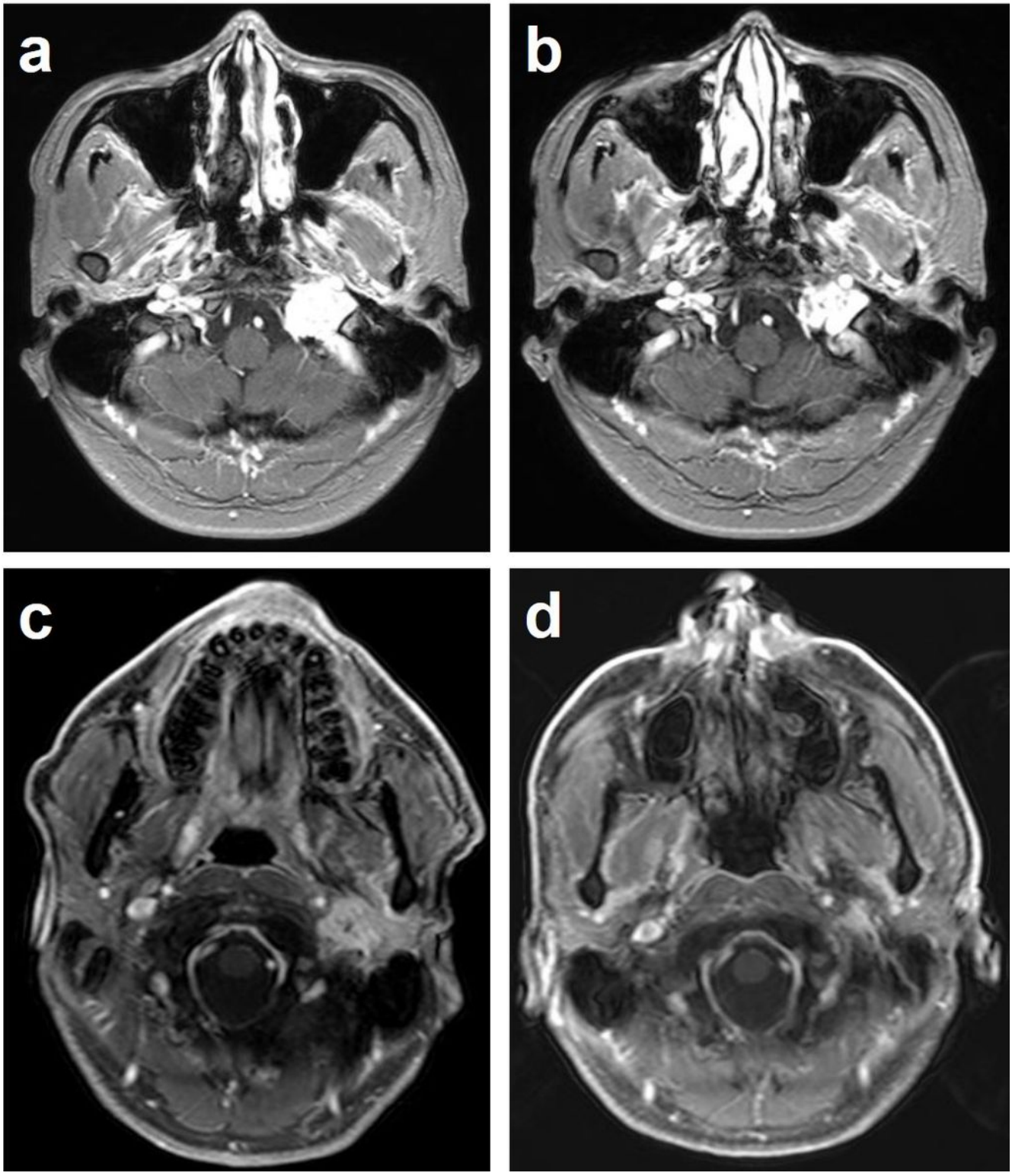


Figure 2

35-year-old male presented with left tongue deviation and dysphagia. We performed CyberKnife therapy (CKT) with the prescribed dose covering 95% of the planning target volume (D95) of 2100cGy in 3 fractions for target tumor volume of 10cc (a). Follow-up MRI at 100 months after CKT showed reduced tumor size (b). 41-year-old male presented with left pulsatile tinnitus and sensory neural hearing

impairment (c). We performed CKT with D95 of 2400cGy in 3 fractions for target tumor volume of 18cc. Follow-up MRI at 75 months after CKT showed reduced tumor size (d).

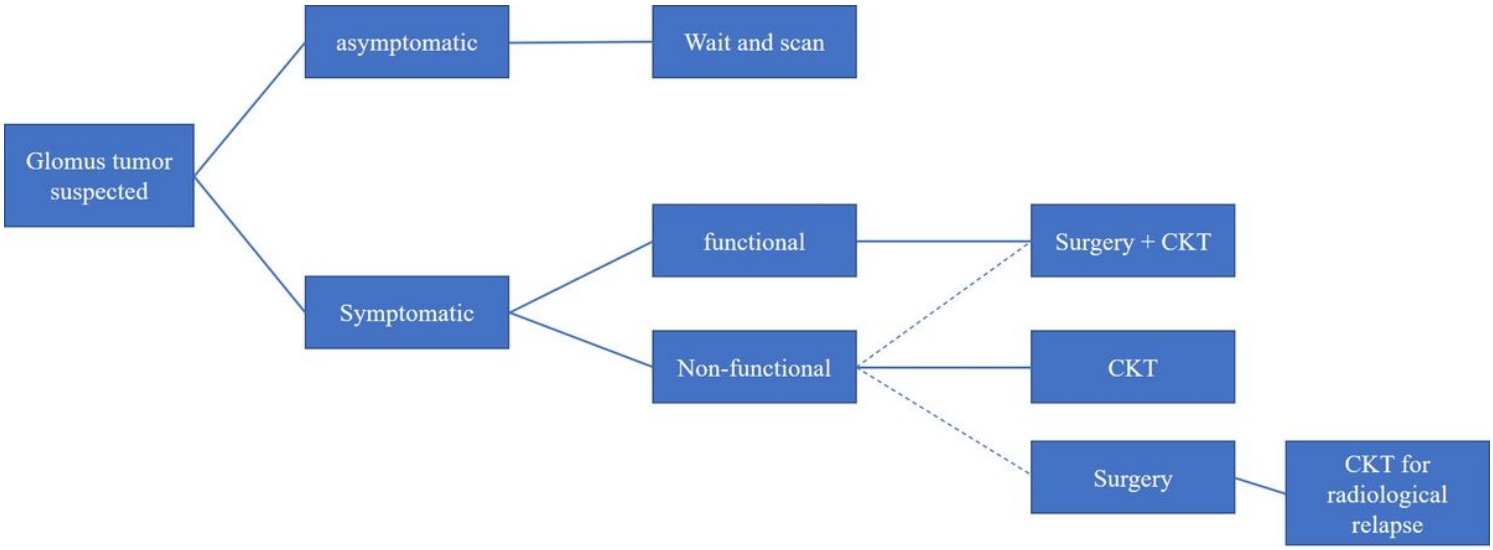


Figure 3

A flow-chart we suggest based on our experience. The management of the head and neck paragangliomas is decided based on its presence of symptoms and the status of hormone production. The symptomatic non-functional paragangliomas may be best treated by upfront CyberKnife therapy (CKT).