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The Role of Image-Guided Robotic Radiosurgery in the Management of Glomus Jugulare Tumors

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Dedicated to my parents and in loving memory of Robert, Hildegund, Irene and Klaus.

Anyone can hold the helm when the sea is calm.

Publilius Syrus

Affidavit

Ehret, Felix

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende kumulative Dissertation mit dem Titel

The Role of Image-Guided Robotic Radiosurgery in the Management of Glomus Jugulare Tumors

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Berlin, 27.11.2020 Felix Ehret

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Contents

Abbreviations

BP	=	Bodily pain
CK	=	CyberKnife
GH	=	General health
GJT	=	Glomus jugulare tumor
GJTs	=	Glomus jugulare tumors
GK	=	GammaKnife
HC	=	Health concepts
LC	=	Local control
LINAC	=	Linear accelerator
MH	=	Mental health
MV	=	Megavolt
PD	=	Progressive disease
PF	=	Physical functioning
QoI	=	Quality of life
RE	=	Role emotional
RP	=	Role physical
RRS	=	Robotic radiosurgery
RS	=	Radiosurgery
SF	=	Social functioning
VT	=	Vitality
WHO	=	World Health Organization

Publications

I. Single-Session Image-Guided Robotic Radiosurgery and Quality of Life for Glomus Jugulare Tumors[1]

II. Image-Guided Robotic Radiosurgery for Glomus Jugulare Tumors – Multicenter Experience and Review of the Literature[2]

Contributions

I, Felix Ehret, was the first author and principal investigator of both publications of this cumulative dissertation[1,2]. No shared first authorships were applied. I was responsible for the study design, planning, literature search, literature review, data collection, data analysis, data monitoring, data interpretation, tables, figures, first manuscript drafts, writing, editing, final editing, submission process and revisions for both studies. Co-authors of both studies were partly involved in the data collection, data interpretation and final editing of the publications.

Introduction

Background

According to the WHO, paragangliomas are vascular, mostly benign, extra-adrenal tumors of sympathetic or parasympathetic paraganglia origin, which can arise in various locations throughout the body[3]. This tumor entity is closely related to the pheochromocytoma, which is defined as an intra-adrenal paraganglioma[3]. Genetic alterations cause a significant proportion of paragangliomas and common tumor sites include the head, neck, thorax, abdomen, pelvis and the adrenal glands in case of pheochromocytomas[4]. Paragangliomas deriving from the adventitial chemoreceptor tissue of the jugular bulb are commonly known as glomus jugulare tumors (GJTs). This term was initially coined by the anatomy professor Stacy Guild from Johns Hopkins University in 1941[5]. Before, these tumors were labeled as a ganglion by Valentin in 1840[6]. With an estimated incidence of one per 1.3 million, GJTs are rare tumors and they only account for a minor proportion of all head and neck tumors[7]. GJTs grow in direct proximity of the jugular foramen, close to the cranial nerves IX, X, XI, the temporal bone and the internal jugular vein. Even though GJTs are considered to be benign tumors, they are capable of locally infiltrating surrounding tissue[8]. Thus, common symptoms of GJTs include lower cranial nerve disorders and range from pulsatile tinnitus, vertigo, hearing loss, dysphagia, dysarthria to – in catecholamine-secreting tumors – cardiovascular complications like tachycardia or hypertension. Hence, the quality of life (QoI) can be significantly decreased in patients with head and neck paragangliomas or GJTs, respectively[9-11]. Rarely, GJTs can metastasize to local lymph nodes or distant organs[8,12-16]. Malignant GJTs account for approximately 3% of tumors[8,12].

In 1934, Seiffert conducted the first reported surgical resection of a glomus jugulare tumor (GJT)[17]. Since then and until the development of radiotherapy, the primary treatment option for GJTs was the surgical resection. Due to the tumor's high vascularization and localization near the skull base and large vessels, surgical procedures may cause severe complications, including posttreatment cranial nerve dysfunctions and, occasionally, significant blood loss due to cerebrovascular injuries, as well as strokes[18-25]. Despite the recent advancements in surgery, the microsurgical tumor extirpation still yields considerable morbidity for patients even if preoperative embolization procedures to reduce the intraoperative bleeding risk are performed[19,20,25]. Non-invasive treatment options came to the fore to overcome this treatment-associated morbidity.

With radiotherapy becoming more and more available since the 1970s, radiation oncologists started to investigate fractionated radiotherapy for head and neck paragangliomas and GJTs.

Radiotherapy studies throughout the past decades reported high local control (LC) rates, usually around 90%, with a more favorable risk profile than surgery[10,19,25-36]. Yet, external body radiotherapy can be associated with radiation-induced complications when doses of 55 to 65 Gy are applied[25]. Usually, doses of 45 Gy over 25 fractions are well-tolerated and have a low risk of complications[19]. Fractionated radiotherapy soon became a recognized treatment alternative to surgery.

To reduce treatment length and field sizes, radiosurgery (RS) was of interest since radiosurgical treatment modalities became more and more available. In 1995, Kida and colleagues firstly reported on the use of RS to treat two GJTs and four lower cranial neurinomas[37]. Since then, numerous retrospective studies have investigated radiosurgical treatments for GJTs throughout the past three decades. Considering the rarity of the tumor, consensus guidelines and large prospective trials with long-term follow-up are not available[19,25]. Most of the radiosurgical work was done with the GammaKnife (GK), a stereotactic treatment unit which was developed by the Swedish neurosurgeon Lars Leksell[2,38,39]. Notably, the GK is limited to the treatment of cranial lesions due to its design and construction. Thus, tumors extending to the lower neck or extracranial neoplasms cannot be treated. Besides, linear accelerator (LINAC)-based radiosurgical treatments and fractionated radiotherapy outcomes were investigated as well, whereas only a few studies analyzed image-guided robotic radiosurgery (RRS) for the treatment of GJTs[1,2,19]. This radiosurgical tool was developed by the neurosurgeon John Adler at Stanford University in the 1990s[40]. The device utilizes a robotic arm which carries a small 6 megavolt (MV) LINAC and can freely move around the patient. No stereotactic frame is needed for treatment delivery. This enables the user to perform frameless stereotactic RS, which is capable of irradiating cranial as well as extracranial tumors[40]. Today, it is built by the Californian company Accuray Incorporated and is commonly known under the name "CyberKnife" (CK). As the reported data for the use of RRS for GJTs is heterogeneous and relatively limited, the overall objective of this thesis was to define and analyze the role of primary and secondary RRS in the management of GJTs and to report essential outcomes for local tumor control, symptom control, radiographic tumor changes and QoI after treatment delivery. To achieve this objective, two dedicated studies were conducted[1,2]. Both publications of this cumulative dissertation were strictly limited to GJTs, which were either histologically proven after biopsy or surgery or the clinical appearance, as well as the imaging findings were sufficient for GJT diagnosis. Moreover, to categorize and assess the respective findings, a comprehensive literature review was done for the use of RS

and RRS for GJTs. Finally, the limitations of both publications regarding study design and data quality were discussed.

Publication I

The first publication investigated the monocentric experience of RRS for GJTs at the European CyberKnife Center Munich[1]. Over a period of 13 years, 53 patients were retrospectively included in the analysis[1]. Thirty-three of them underwent primary treatment with RRS[1]. This study analyzed the outcomes and QoI data after single-session RRS[1]. The results show that RRS is a safe, reliable and efficient tool for the primary and secondary treatment of GJT[1]. After a median follow-up of 38 months, an overall LC of 98% was achieved[1]. Only one of the 53 patients developed a local recurrence[1]. The literature review for RRS showed that most of the reported data is heterogeneous and many studies included not only GJTs but also other paragangliomas, e.g. glomus jugulotympanicum, glomus tympanicum and carotid body tumors, in their analyses[1]. The clinical outcomes were comparable with other radiosurgical studies, as most of the patients experienced symptom control or pretreatment deficit improvements[1,2]. LC rates were as high as reported elsewhere in the literature[1,19,25]. To the best of our knowledge, this was the first study to report standardized QoI data before and after treatment delivery[1]. So far, only a few studies have investigated the QoI in head and neck paragangliomas, including GJTs, most of them by mailing questionnaires after treatment delivery[11,41,42]. In the first publication, the QoI was measured by the SF-12, the shortened version of the SF-36[43,44]. The SF-12 is a well-established and validated questionnaire to assess the QoI for eight different health concepts (HC)[43-45]. Patients were asked to answer the SF-12 before treatment and during follow-up. No statistically significant decrease in any of the measured HC was found either at first or last follow-up[1]. At first follow-up, six months after treatment delivery, bodily pain (BP) significantly improved compared to the pretreatment status ($p = 0.04$)[1]. Moreover, there was a trend towards improvement in mental health (MH), which failed to reach significance ($p = 0.08$)[1]. The only decrease in absolute HC values was related to role physical (RP) but was not significant ($p = 0.31$)[1]. Analysis of the SF-12 outcomes at the last follow-up, after a median of 38 months, showed no significant changes in any of the eight HC[1]. Yet, trends towards improvements in RP and vitality (VT) were seen ($p = 0.06$ and $p = 0.08$)[1]. To conclude, the first publication proved the safety and efficacy of single-session RRS for GJTs in a single-center analysis. LC rates and symptom control were high, whereas no severe complications or treatment-related mortality had been observed[1]. Finally, the study showed that patients' QoI remains stable or even improves after treatment delivery[1].

Publication II

The second publication had the objective to verify the initial findings of the single-center study with a larger sample size. Additionally, further objectives included the investigation of prognostic factors for symptom control and tumor volume decrease. Finally, a review of the radiosurgical literature regardless of the utilized radiosurgical technique (GK, CK, LINAC) was conducted. Given the epidemiology of GJTs, only a multicenter study was able to provide these insights and to account for biases given the single-center design of the first study. Besides the European Cyberknife Center, five more dedicated centers in Germany participated in the multicenter study, namely Berlin, Cologne, Erfurt, Soest and Göppingen[2]. As the role of fractionation in RS for GJTs is unclear, the data of patients with multisession RRS were included in the second publication to enhance the total sample size and to investigate the potential effects of fractionated treatments. Patients undergoing RRS up to a total of five fractions were eligible for enrollment. Usually, larger GJTs are treated in up to five sessions with good success[46-49].

In the second publication, a total of 101 patients from six centers and their outcomes were analyzed[2]. Sixty-two of them received their primary treatment with RRS[2]. With a median follow-up of 35 months, the follow-up was slightly shorter in comparison with the single-center analysis[1,2]. Yet, comparable results in regard to LC and symptom control were observed[2]. The overall LC at last follow-up was 99%[2]. The posttreatment tumor volume was found to be significantly smaller at last follow-up for primarily and secondarily treated tumors as well as all patients[2]. Notably, only one patient had experienced a progressive disease (PD), the same case which was previously included in the single-center analysis[1,2]. No patients from centers outside of Munich reported cases of PD. The majority of included patients suffering from pretreatment deficits, 89 of 96, had stable symptoms or experienced clinical improvements after treatment delivery[2]. A total of five patients did not report symptoms at the time of treatment delivery and remained stable during their follow-up[2]. Only 13 patients were treated in up to five sessions[2]. Given this small number of patients treated with more than one fraction, no dedicated comparisons with single-session treatments in regard to LC and symptom control were conducted.

To investigate prognostic factors for posttreatment tumor volume reduction, toxicity and symptom improvement, linear and logistic regression analyses were performed. Pretreatment tumor volume was found to be a significant predictor of posttreatment tumor volume change (measured in cubic centimeters). Besides, no predictors for symptom improvement and

toxicity have been identified[2]. Only a few studies have investigated prognostic factors for GJT treatment outcomes so far[2,50-56]. One report identified that a higher number of isocenters for GK-based RS and the absence of trigeminal nerve dysfunctions at treatment correlate with progression-free tumor survival[50]. A study from 2017 showed that a higher marginal dose is associated with an increased risk of tumor progession[55]. For symptom control or pretreatment deficit improvements, one study found in a univariate analysis that pretreatment cranial nerve disorders are associated with lowered chances of posttreatment symptom improvement[51]. Moreover, prior surgical resection was shown to correlate with symptom persistence when compared to non-surgical patients[56]. Overall, reliable and reproducible prognostic factors remain unknown and hinder the development of consensus guidelines for GJT patients.

Since a comprehensive review for RRS in the management of GJTs was already completed in the first publication, the second study had the objective of analyzing the radiosurgical literature since 2000, regardless of the chosen treatment modality[1,2]. Through a PubMed-based literature research, 29 studies reporting the radiosurgical primary and secondary treatment of GJTs were identified and analyzed[2,39,46,50-77]. Most of the radiosurgical reports included patients undergoing GK-based RS[2]. Moreover, most patients included in the analyzed studies received single-session RS as their primary treatment[2]. Reported LC rates were high, with a minority of patients suffering from complications after treatment[2]. Ultimately, RS led to symptom control or pretreatment deficit improvements in most patients. Overall, the results of the literature review were in agreement with the findings of the first and second publication[1,2]. No evidence was found that RRS might be inferior to GK- or LINAC-based RS[2].

Discussion

This cumulative dissertation had the objective of defining the role of RRS in the management of GJTs. The first publication was the largest investigating single-session RRS for GJTs and the first to report standardized QoI analyses before and after treatment with RS[1]. The second publication comprised the second-largest radiosurgical series of patients treated for GJTs and the third to use a multicenter design for GJT RS[2]. The results of both studies showed RRS to be safe and effective for the primary and secondary treatment of GJTs[1,2]. These findings are comparable to the radiosurgical literature available and suggest that RRS may be considered for the primary and secondary treatment for the majority of GJTs[1,2]. Especially the stable and partially improving QoI results after treatment delivery are vital to improve clinical decision-making and to guide GJT patients who are eligible to undergo surgical tumor resection or radiotherapy. It is important to note that surgical treatment options yield a larger treatment-related morbidity than RS and radiotherapy but may achieve comparable LC rates[19,20,25]. Nevertheless, surgery is considered to play an essential role for catecholamine-secreting and malignant GJTs, as well as for young patients with high life expectancy[19,25]. In addition, some studies have recommended surgical resection for small to medium-sized GJTs[78-80]. In regard to the available literature, RS, including RRS, seems to have a slightly better LC than radiotherapy and may cause fewer complications, irrespective of the treatment modality utilized (GK, CK, LINAC)[2,19,25]. However, radiotherapy may be used for GJT patients if RS is not available[19]. Both techniques have advantageous risk profiles compared to surgery and the risk of radiation-induced malignancies and persistent complications is low[19,25,81]. Given the lack of reports investigating multidisciplinary treatments, the dedicated roles of radiotherapy, RS, surgery and combinations of them remain unclear.

Taking the median follow-up durations of both publications into consideration, more analyses with longer follow-up are needed to determine whether the present findings are long-lasting. This is particularly important as GJT recurrences can occur many years after treatment delivery[19,25,38,82,83]. Other limitations of both publications include their retrospective nature, thereby increasing the risk for selection and reporting biases, lack of histopathological diagnosis in the majority of patients and lack of detailed follow-up information for pretreatment deficits, as well as classification systems (e. g. House-Brackmann, audiogram, Fisch classification). Despite these limitations, this dissertation, including both publications, provides evidence that RRS can play a central role in the management of GJTs, especially for patients not suitable for surgical resection. To evaluate not only the role of RRS but also RS further, prospective studies are needed, addressing the inherent limitations of the publications

described and reviewed here. Patient-reported outcomes, like QoI analyses should be implemented to guide further decision-making. Finally, trials comparing surgery with RS or radiotherapy might help to establish consensus guidelines for GJT management, which would ultimately advance clinical care for patients.

Conclusion

Both studies showed RRS to be a safe and efficient treatment option for GJTs. The results of the primary and secondary treatment for GJTs are consistent, while the QoI of patients remains stable and tends to improve after treatment delivery. RRS achieves comparable results to other radiosurgical techniques while demonstrating a low rate of treatment-associated complications. RRS may be considered as a primary treatment option for most GJTs.

Summary

Glomus jugulare tumors (GJTs) are rare head and neck paragangliomas originating from the paraganglia of the jugular bulb. These tumors may cause significant morbidity, a decline in patients' quality of life (QoI) and remain challenging to treat surgically given their localization and vascularization. Thus, non-invasive treatment options can be advantageous, not only for patients not suitable for surgical resection. Radiosurgery (RS) for GJTs has been of recent interest due to its efficacy and safety. So far, only limited data is available on the use of image-guided robotic radiosurgery (RRS) for treatment of GJTs. In this cumulative dissertation, the role of RRS in the management of GJTs was investigated with two studies, one single-center study and a subsequent multicenter trial. Results of both analyses, including a comprehensive literature review, showed RRS to be an effective and safe tool for the primary and secondary treatment of GJTs. Local control (LC) and symptom control rates are high and comparable to the radiosurgical results reported in the literature. Moreover, QoI analyses of SF-12 data showed that patients have a stable or even improved QoI after RRS treatment delivery. Pretreatment tumor volume had a significant impact on posttreatment tumor volume reduction. No predictive factors for symptom improvement and toxicity were found. Overall, the results of both studies suggest RRS to be a primary treatment option for most GJTs.

Glomus jugulare Tumoren (GJT) sind seltene Paragangliome der Schädelbasis, welche aus den (para)sympathischen Zellen im Bereich des Bulbus venae jugularis entspringen. Aufgrund ihrer

Lokalisation können diese Tumoren starke Beschwerden und eine eingeschränkte Lebensqualität bei betroffenen Patienten herbeiführen. Aufgrund dessen und durch die ausgeprägte Vaskularisation sind die Tumoren nach wie vor chirurgisch nur eingeschränkt zu behandeln. Folglich können nicht-invasive Behandlungsoptionen von Vorteil sein, vor allem für Patienten, die sich keiner Operation unterziehen können bzw. wollen. Aufgrund ihrer Effektivität und Sicherheit bei der Behandlung von GJT ist die Radiochirurgie zunehmend in den Fokus des Interesses gerückt. Derzeit gibt es nur eingeschränkte Daten zum Gebrauch der bildgeführten robotischen Radiochirurgie zur Behandlung von GJT. In dieser kumulativen Dissertation wurde der Stellenwert der bildgeführten robotischen Radiochirurgie für die Behandlung von GJT im Rahmen zweier Studien untersucht – zuerst in einer monozentrischen Analyse, in der Folge anhand einer multizentrischen Studie. Die Ergebnisse beider Untersuchungen einschließlich einer umfassenden Literaturanalyse zeigen, dass die robotische Radiochirurgie eine effektive und sichere Behandlungsmethode sowohl für die primäre, als auch sekundäre Behandlung von GJT darstellt. Die Lokal- als auch Symptomkontrolle sind hoch und vergleichbar mit den radiochirurgischen Ergebnissen, die in der bisherigen Literatur beschrieben sind. Des Weiteren zeigten die Analysen der SF-12 Daten, dass Patienten nach der Behandlung eine stabile oder sogar verbesserte Lebensqualität genießen. Das prätherapeutische Tumorvolumen hatte signifikanten Einfluss auf den posttherapeutischen Tumorvolumenrückgang. Prädiktive Faktoren zur Beschwerdebesserung und Toxizität wurden nicht gefunden. Die Ergebnisse beider Studien legen nahe, dass die robotische Radiochirurgie eine primäre Behandlungsoption für den Großteil der GJT darstellen kann.

Publication I

Single-Session Image-Guided Robotic Radiosurgery and Quality of Life for Glomus Jugulare Tumors[1]

Ehret F, Kufeld M, Fürweger C, et al.

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Publication II

Image-Guided Robotic Radiosurgery for Glomus Jugulare Tumors – Multicenter Experience and Review of the Literature[2]

Ehret F, Kufeld M, Fürweger C, et al.

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PMID: 32851752

References

1. Ehret F, Kufeld M, Fürweger C, et al. Single-session image-guided robotic radiosurgery and quality of life for glomus jugulare tumors. *Head & neck* 2020; **42**(9): 2421-30.
2. Ehret F, Kufeld M, Fürweger C, et al. Image-guided robotic radiosurgery for glomus jugulare tumors-Multicenter experience and review of the literature. *Head & neck* 2020.
3. DeLellis RA. Pathology and genetics of tumours of endocrine organs: IARC; 2004.
4. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. *Nat Rev Endocrinol* 2015; **11**(2): 101-11.
5. Guild SR. The glomus jugulare, a nonchromaffin paraganglion, in man. *The Annals of otology, rhinology, and laryngology* 1953; **62**(4): 1045-71; concld.
6. Bickerstaff ER, Howell JS. The neurological importance of tumours of the glomus jugulare. *Brain : a journal of neurology* 1953; **76**(4): 576-93.
7. Moffat DA, Hardy DG. Surgical management of large glomus jugulare tumours: infra- and trans-temporal approach. *J Laryngol Otol* 1989; **103**(12): 1167-80.
8. Gulya AJ. The glomus tumor and its biology. *The Laryngoscope* 1993; **103**(11 Pt 2 Suppl 60): 7-15.
9. Havekes B, van der Klaauw AA, Hoftijzer HC, et al. Reduced quality of life in patients with head-and-neck paragangliomas. *Eur J Endocrinol* 2008; **158**(2): 247-53.
10. van Hulsteijn LT, Louisse A, Havekes B, et al. Quality of life is decreased in patients with paragangliomas. *Eur J Endocrinol* 2013; **168**(5): 689-97.
11. Patel NS, Link MJ, Tombers NM, Pollock BE, Carlson ML. Quality of Life in Jugular Paraganglioma Following Radiosurgery. *Otol Neurotol* 2019; **40**(6): 820-5.
12. Lee JH, Barich F, Karnell LH, et al. National Cancer Data Base report on malignant paragangliomas of the head and neck. *Cancer* 2002; **94**(3): 730-7.
13. Wolter NE, Adil E, Irace AL, et al. Malignant glomus tumors of the head and neck in children and adults: Evaluation and management. *The Laryngoscope* 2017; **127**(12): 2873-82.
14. Folpe AL, Fanburg-Smith JC, Miettinen M, Weiss SW. Atypical and malignant glomus tumors: analysis of 52 cases, with a proposal for the reclassification of glomus tumors. *Am J Surg Pathol* 2001; **25**(1): 1-12.
15. Brathwaite CD, Poppiti RJ, Jr. Malignant glomus tumor. A case report of widespread metastases in a patient with multiple glomus body hamartomas. *Am J Surg Pathol* 1996; **20**(2): 233-8.
16. Hamidi O, Young WF, Jr., Iñiguez-Ariza NM, et al. Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years. *J Clin Endocrinol Metab* 2017; **102**(9): 3296-305.
17. Lundgren N. Tympanic body tumours in the middle ear; tumours of carotid body type. *Acta oto-laryngologica* 1949; **37**(4): 367-79, illust.
18. Hallett JW, Jr., Nora JD, Hollier LH, Cherry KJ, Jr., Pairolero PC. Trends in neurovascular complications of surgical management for carotid body and cervical paragangliomas: a fifty-year experience with 153 tumors. *Journal of vascular surgery* 1988; **7**(2): 284-91.
19. Lieberson RE, Adler JR, Soltys SG, Choi C, Gibbs IC, Chang SD. Stereotactic radiosurgery as the primary treatment for new and recurrent paragangliomas: is open surgical resection still the treatment of choice? *World neurosurgery* 2012; **77**(5-6): 745-61.
20. Gottfried ON, Liu JK, Couldwell WT. Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. *Neurosurgical focus* 2004; **17**(2): E4.
21. Bacciu A, Medina M, Ait Mimoune H, et al. Lower cranial nerves function after surgical treatment of Fisch Class C and D tympanojugular paragangliomas. *European Archives of Oto-Rhino-Laryngology* 2015; **272**(2): 311-9.
22. Wanna GB, Sweeney AD, Haynes DS, Carlson ML. Contemporary management of jugular paragangliomas. *Otolaryngologic clinics of North America* 2015; **48**(2): 331-41.
23. Kaylie DM, O'Malley M, Aulino JM, Jackson CG. Neurotologic surgery for glomus tumors. *Otolaryngologic clinics of North America* 2007; **40**(3): 625-49, x.
24. van der Mey AG, Frijns JH, Cornelisse CJ, et al. Does intervention improve the natural course of glomus tumors? A series of 108 patients seen in a 32-year period. *The Annals of otology, rhinology, and laryngology* 1992; **101**(8): 635-42.

25. Suarez C, Rodrigo JP, Bodeker CC, et al. Jugular and vagal paragangliomas: Systematic study of management with surgery and radiotherapy. *Head & neck* 2013; **35**(8): 1195-204.
26. Huy PT, Kania R, Duet M, Dessard-Diana B, Mazeron JJ, Benhamed R. Evolving concepts in the management of jugular paraganglioma: a comparison of radiotherapy and surgery in 88 cases. *Skull Base* 2009; **19**(1): 83-91.
27. Krych AJ, Foote RL, Brown PD, Garces YI, Link MJ. Long-term results of irradiation for paraganglioma. *Int J Radiat Oncol Biol Phys* 2006; **65**(4): 1063-6.
28. Pryzant RM, Chou JL, Easley JD. Twenty year experience with radiation therapy for temporal bone chemodectomas. *Int J Radiat Oncol Biol Phys* 1989; **17**(6): 1303-7.
29. Schild SE, Foote RL, Buskirk SJ, et al. Results of radiotherapy for chemodectomas. *Mayo Clin Proc* 1992; **67**(6): 537-40.
30. Cole JM, Beiler D. Long-term results of treatment for glomus jugulare and glomus vagale tumors with radiotherapy. *The Laryngoscope* 1994; **104**(12): 1461-5.
31. de Jong AL, Coker NJ, Jenkins HA, Goepfert H, Alford BR. Radiation therapy in the management of paragangliomas of the temporal bone. *Am J Otol* 1995; **16**(3): 283-9.
32. Pemberton LS, Swindell R, Sykes AJ. Radical radiotherapy alone for glomus jugulare and tympanicum tumours. *Oncol Rep* 2005; **14**(6): 1631-3.
33. Hinerman RW, Amdur RJ, Morris CG, Kirwan J, Mendenhall WM. Definitive radiotherapy in the management of paragangliomas arising in the head and neck: a 35-year experience. *Head & neck* 2008; **30**(11): 1431-8.
34. Lassen-Ramshad Y, Ozyar E, Alanyali S, et al. Paraganglioma of the head and neck region, treated with radiation therapy, a Rare Cancer Network study. *Head & neck* 2019; **41**(6): 1770-6.
35. Lightowlers S, Benedict S, Jefferies SJ, et al. Excellent local control of paraganglioma in the head and neck with fractionated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010; **22**(5): 382-9.
36. van Hulsteijn LT, Corssmit EP, Coremans IE, Smit JW, Jansen JC, Dekkers OM. Regression and local control rates after radiotherapy for jugulotympanic paragangliomas: systematic review and meta-analysis. *Radiother Oncol* 2013; **106**(2): 161-8.
37. Kida Y, Kobayashi T, Tanaka T, Oyama H, Niwa M. [A new strategy for the treatment of jugular foramen tumors using radiosurgery]. *No shinkei geka Neurological surgery* 1995; **23**(8): 671-5.
38. Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; **81**(4): e497-502.
39. Patel NS, Carlson ML, Pollock BE, et al. Long-term tumor control following stereotactic radiosurgery for jugular paraganglioma using 3D volumetric segmentation. *J Neurosurg* 2018: 1-9.
40. Adler JR, Jr., Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL. The Cyberknife: a frameless robotic system for radiosurgery. *Stereotactic and functional neurosurgery* 1997; **69**(1-4 Pt 2): 124-8.
41. Galland-Girodet S, Maire JP, De-Mones E, et al. The role of radiation therapy in the management of head and neck paragangliomas: impact of quality of life versus treatment response. *Radiother Oncol* 2014; **111**(3): 463-7.
42. Patel NS, Link MJ, Driscoll CLW, Pollock BE, Lohse CM, Carlson ML. Hearing Outcomes After Stereotactic Radiosurgery for Jugular Paraganglioma. *Otol Neurotol* 2018; **39**(1): 99-105.
43. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care* 1996; **34**(3): 220-33.
44. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998; **51**(11): 1171-8.
45. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med* 1997; **19**(2): 179-86.
46. Hurmuz P, Cengiz M, Ozyigit G, et al. Robotic stereotactic radiosurgery in patients with unresectable glomus jugulare tumors. *Technology in cancer research & treatment* 2013; **12**(2): 109-13.
47. Chun SG, Nedzi LA, Choe KS, et al. A retrospective analysis of tumor volumetric responses to five-fraction stereotactic radiotherapy for paragangliomas of the head and neck (glomus tumors). *Stereotactic and functional neurosurgery* 2014; **92**(3): 153-9.
48. Tuniz F, Soltys SG, Choi CY, et al. Multisession cyberknife stereotactic radiosurgery of large, benign cranial base tumors: preliminary study. *Neurosurgery* 2009; **65**(5): 898-907; discussion

49. Tosun I, Atalar B, Sahin B, et al. Robotic radiosurgery of head and neck paragangliomas: a single institution experience. *Asia-Pacific journal of clinical oncology* 2018; **14**(2): e3-e7.
50. Sheehan JP, Tanaka S, Link MJ, et al. Gamma Knife surgery for the management of glomus tumors: a multicenter study. *J Neurosurg* 2012; **117**(2): 246-54.
51. Sallabanda K, Barrientos H, Isernia Romero DA, et al. Long-term outcomes after radiosurgery for glomus jugulare tumors. *Tumori* 2018; **104**(4): 300-6.
52. Ibrahim R, Ammori MB, Yianni J, Grainger A, Rowe J, Radatz M. Gamma Knife radiosurgery for glomus jugulare tumors: a single-center series of 75 cases. *J Neurosurg* 2017; **126**(5): 1488-97.
53. Gandia-Gonzalez ML, Kusak ME, Moreno NM, Sarraga JG, Rey G, Alvarez RM. Jugulotympanic paragangliomas treated with Gamma Knife radiosurgery: a single-center review of 58 cases. *J Neurosurg* 2014; **121**(5): 1158-65.
54. Sharma M, Meola A, Bellamkonda S, et al. Long-Term Outcome Following Stereotactic Radiosurgery for Glomus Jugulare Tumors: A Single Institution Experience of 20 Years. *Neurosurgery* 2018; **83**(5): 1007-14.
55. Winford TW, Dorton LH, Browne JD, Chan MD, Tatter SB, Oliver ER. Stereotactic Radiosurgical Treatment of Glomus Jugulare Tumors. *Otol Neurotol* 2017; **38**(4): 555-62.
56. Wakefield DV, Venable GT, VanderWalde NA, et al. Comparative Neurologic Outcomes of Salvage and Definitive Gamma Knife Radiosurgery for Glomus Jugulare: A 20-Year Experience. *J Neurol Surg B Skull Base* 2017; **78**(3): 251-5.
57. Tripathi M, Rekhapalli R, Batish A, et al. Safety and Efficacy of Primary Multisession Dose Fractionated Gamma Knife Radiosurgery for Jugular Paragangliomas. *World neurosurgery* 2019; **131**: e136-e48.
58. Gigliotti MJ, Hasan S, Liang Y, Chen D, Fuhrer R, Wegner RE. A 10-year experience of linear accelerator-based stereotactic radiosurgery/radiotherapy (SRS/SRT) for paraganglioma: A single institution experience and review of the literature. *J Radiosurg SBRT* 2018; **5**(3): 183-90.
59. Hafez RFA, Morgan MS, Fahmy OM, Hassan HT. Long-term effectiveness and safety of stereotactic gamma knife surgery as a primary sole treatment in the management of glomus jagulare tumor. *Clin Neurol Neurosurg* 2018; **168**: 34-7.
60. Dobberpuhl MR, Maxwell S, Feddock J, St Clair W, Bush ML. Treatment Outcomes for Single Modality Management of Glomus Jugulare Tumors With Stereotactic Radiosurgery. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology* 2016; **37**(9): 1406-10.
61. El Majdoub F, Hunsche S, Igressa A, Kocher M, Sturm V, Maarouf M. Stereotactic LINAC-Radiosurgery for Glomus Jugulare Tumors: A Long-Term Follow-Up of 27 Patients. *PLoS One* 2015; **10**(6): e0129057.
62. Sager O, Beyzadeoglu M, Dincoglan F, et al. Evaluation of linear accelerator-based stereotactic radiosurgery in the management of glomus jugulare tumors. *Tumori* 2014; **100**(2): 184-8.
63. de Andrade EM, Brito JR, Mario SD, de Melo SM, Benabou S. Stereotactic radiosurgery for the treatment of Glomus Jugulare Tumors. *Surg Neurol Int* 2013; **4**(Suppl 6): S429-35.
64. Chen PG, Nguyen JH, Payne SC, Sheehan JP, Hashisaki GT. Treatment of glomus jugulare tumors with gamma knife radiosurgery. *The Laryngoscope* 2010; **120**(9): 1856-62.
65. Genc A, Bicer A, Abacioglu U, Peker S, Pamir MN, Kilic T. Gamma knife radiosurgery for the treatment of glomus jugulare tumors. *J Neurooncol* 2010; **97**(1): 101-8.
66. Navarro Martin A, Maitz A, Grills IS, et al. Successful treatment of glomus jugulare tumours with gamma knife radiosurgery: clinical and physical aspects of management and review of the literature. *Clin Transl Oncol* 2010; **12**(1): 55-62.
67. Ganz JC, Abdelkarim K. Glomus jugulare tumours: certain clinical and radiological aspects observed following Gamma Knife radiosurgery. *Acta Neurochir (Wien)* 2009; **151**(5): 423-6.
68. Miller JP, Semaan M, Einstein D, Megerian CA, Maciunas RJ. Staged Gamma Knife radiosurgery after tailored surgical resection: a novel treatment paradigm for glomus jugulare tumors. *Stereotactic and functional neurosurgery* 2009; **87**(1): 31-6.
69. Sharma MS, Gupta A, Kale SS, Agrawal D, Mahapatra AK, Sharma BS. Gamma knife radiosurgery for glomus jugulare tumors: therapeutic advantages of minimalism in the skull base. *Neurol India* 2008; **56**(1): 57-61.

70. Lim M, Bower R, Nangiana JS, Adler JR, Chang SD. Radiosurgery for glomus jugulare tumors. *Technology in cancer research & treatment* 2007; **6**(5): 419-23.
71. Bitaraf MA, Alikhani M, Tahsili-Fahadan P, et al. Radiosurgery for glomus jugulare tumors: experience treating 16 patients in Iran. *J Neurosurg* 2006; **105 Suppl**: 168-74.
72. Feigl GC, Horstmann GA. Intracranial glomus jugulare tumors: volume reduction with Gamma Knife surgery. *J Neurosurg* 2006; **105 Suppl**: 161-7.
73. Gerosa M, Visca A, Rizzo P, Foroni R, Nicolato A, Bricolo A. Glomus jugulare tumors: the option of gamma knife radiosurgery. *Neurosurgery* 2006; **59**(3): 561-9; discussion -9.
74. Poznanovic SA, Cass SP, Kavanagh BD. Short-term tumor control and acute toxicity after stereotactic radiosurgery for glomus jugulare tumors. *Otolaryngol Head Neck Surg* 2006; **134**(3): 437-42.
75. Feigenberg SJ, Mendenhall WM, Hinerman RW, Amdur RJ, Friedman WA, Antonelli PJ. Radiosurgery for paraganglioma of the temporal bone. *Head & neck* 2002; **24**(4): 384-9.
76. Eustacchio S, Trummer M, Unger F, Schrottner O, Sutter B, Pendl G. The role of Gamma Knife radiosurgery in the management of glomus jugular tumours. *Acta Neurochir Suppl* 2002; **84**: 91-7.
77. Saringer W, Khayal H, Ertl A, Schoeggl A, Kitz K. Efficiency of gamma knife radiosurgery in the treatment of glomus jugulare tumors. *Minim Invasive Neurosurg* 2001; **44**(3): 141-6.
78. Forest JA, 3rd, Jackson CG, McGrew BM. Long-term control of surgically treated glomus tympanicum tumors. *Otol Neurotol* 2001; **22**(2): 232-6.
79. Jackson CG, Glasscock ME, 3rd, Harris PF. Glomus Tumors. Diagnosis, classification, and management of large lesions. *Arch Otolaryngol* 1982; **108**(7): 401-10.
80. Lenarz T, Plinkert PK. [Glomus tumors of the temporal bone--surgical concept and results]. *Laryngorhinootologie* 1992; **71**(3): 149-57.
81. Pollock BE, Link MJ, Stafford SL, Parney IF, Garces YI, Foote RL. The Risk of Radiation-Induced Tumors or Malignant Transformation After Single-Fraction Intracranial Radiosurgery: Results Based on a 25-Year Experience. *Int J Radiat Oncol Biol Phys* 2017; **97**(5): 919-23.
82. Pollock BE, Foote RL. The evolving role of stereotactic radiosurgery for patients with skull base tumors. *J Neurooncol* 2004; **69**(1-3): 199-207.
83. Shapiro S, Kellermeyer B, Ramadan J, Jones G, Wiseman B, Cassis A. Outcomes of Primary Radiosurgery Treatment of Glomus Jugulare Tumors: Systematic Review With Meta-analysis. *Otol Neurotol* 2018; **39**(9): 1079-87.

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Curriculum vitae

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