¬3-session vs 5-session dose-fractionation of stereotactic radiosurgery in Glomus Jugulare: Protocol for a Randomized Clinical Trial

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Table of Contents

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Abstract

Background: Gamma Knife stereotactic radiosurgery (SRS) is a pivotal therapeutic strategy for managing jugular paragangliomas (JP) due to the tumor's vascularity and the intricacies of regional anatomy. Noteworthy is the comparison between limited-session dose fractionation SRS and multisession fractionated Gamma Knife SRS, with the former being linked to a higher incidence of adverse effects on at-risk organs and the latter may be accompanied by lower rate of tumor control.

Objective: The primary objective is to assess tumor size post-intervention, evaluated through MRI sequences at 6-month and 1-year intervals. Secondary objectives include alleviating tumor-associated symptoms, and documenting severe adverse outcomes.

Methods: This document outlines a trial protocol for a comparative study evaluating the efficacy of 3-session versus 5-session fractionation in Gamma Knife SRS for JP. In this single-center prospective randomized clinical trial, 40 eligible JP patients will be randomly assigned to receive either three sessions of Gamma Knife SRS (cumulative radiation dose: 18-21 GY) or five sessions (cumulative radiation dose: 21-25 GY).

Results: As of March 2024, the patient screening process has not begun, and no participants have been enrolled in the trial.

Conclusions: Prior research reveals a significant gap in knowledge, hindering a comprehensive comparison of gamma knife radiosurgery dosage fractionations in JP. This protocol seeks to address this gap by investigating the impact of 3 sessions versus 5 sessions of dose-fractionated Gamma Knife SRS on JP. Clinical Trial: #To be registered#

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Running title: Dose fractionation in GJT SRS

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Abstract

Background: Gamma Knife stereotactic radiosurgery (SRS) is a pivotal therapeutic strategy for managing jugular paragangliomas (JP) due to the tumor's vascularity and the intricacies of regional anatomy. Noteworthy is the comparison between limited-session dose fractionation SRS and multisession fractionated Gamma Knife SRS, with the former being linked to a higher incidence of adverse effects on at-risk organs and the latter may be accompanied by lower rate of tumor control.

Objective: This document outlines a trial protocol for a comparative study evaluating the efficacy of 3-session versus 5-session fractionation in Gamma Knife SRS for JP.

Methods: In this stage 3 single-center prospective randomized clinical trial, 40 eligible JP patients will be randomly assigned to receive either three sessions of Gamma Knife SRS (cumulative radiation dose: 18-21 Gray (Gy)) or five sessions (cumulative radiation dose: 21-25 GY).

Results: The primary objective is to assess tumor size post-intervention, evaluated through MRI sequences at 6-month and 1-year intervals. Secondary objectives include alleviating tumor-associated symptoms, and documenting severe adverse outcomes.

Conclusions: Prior research reveals a significant gap in knowledge, hindering a comprehensive comparison of gamma knife radiosurgery dosage fractionations in JP. This protocol seeks to address this gap by investigating the impact of 3 sessions versus 5 sessions of dose-fractionated Gamma Knife SRS on JP.

Keywords: Jugular paraganglioma; Glomus jugulare; Fractionated radiosurgery; Leksell Gamma Knife

Introduction

Jugular paragangliomas, also known as Glomus jugulare, are slow-growing benign tumors which arise from paraganglia of the head and neck on the superior surface of jugular bulb within the jugular foramen [1]. These rare tumors occur predominantly in women with an estimated incidence of 1 to 3 per 100,000 individuals [2]. Jugular paragangliomas originate from parasympathetic paraganglial system and may present with lower cranial nerve dysfunction and local soft tissue infiltration.

The management of jugular paragangliomas poses a complex challenge, often requiring a multidisciplinary approach. Treatment options include observation, surgical resection, radiotherapy, or a combination thereof. Traditionally, jugular paragangliomas are treated through surgical resection with or without embolization or through radiotherapy. Apparently , Gamma Knife Stereotactic Radiosurgery (SRS) has emerged as a valuable modality, offering a non-invasive and precise means of delivering focused radiation to the tumor [3].

SRS, utilizing highly targeted radiation beams, has shown efficacy in controlling tumor growth while minimizing damage to surrounding healthy tissues. However, the optimal radiation dose for jugular paragangliomas remains an area of active investigation [4]. While standard single-session SRS protocols have been employed, concerns regarding potential side effects of radiation to organs at risk such as cranial nerve deficits and hearing loss, prompt a reevaluation of dose fractionation strategies [5]. Especially so, considering no previous works evaluated this notion in a randomized and structured manner. This paper outlines a trial protocol for a non-inferiority comparative study investigating the efficacy of 5-session fractionation vs. 3-session fractionation in Gamma Knife SRS for jugular paragangliomas. We aim to determine whether further fractionation can mitigate

side effects associated with conventional SRS doses, optimizing patient outcomes.

Methods

Study center and recruitment process

All patients with an established diagnosis of jugular paraganglioma who are referred to the radiotherapy department - Gamma Knife Center of Yas Hospital (Tehran, Iran), affiliated with Tehran University of Medical Sciences, will undergo a thorough clinical evaluation by the scientific review panel within the trial steering committee, composed of certified physicians and specialists from radio-oncology and neurosurgery departments.

A joint evaluation will consider the patient's eligibility for radiosurgery upon obtaining adequate clinical and imaging data and patient history. If the final decision cannot be rendered with the existing data, the patient will be reassessed in future sessions following further data acquisition. Following initial approval, patients will undergo rigorous imaging studies required for contour delineation.

The current protocol requires non-contrast enhanced computed tomography (CT) scans with 1mm thin slices, T1-weighted, T1-weighted contrast-enhanced (Gadolinium-based contrast), and T2-weighted magnetic resonance imaging (MRI) sequences, time of flight (ToF) magnetic resonance angiography and magnetic resonance venography (MRV) for all eligible patients. Imaging data will be used for the Gamma Knife treatment planning system (GammaPlan®, Elekta, Sweden). The baseline auditory function of the patients will be evaluated with standardized audiometry tests (Pure tone audiometry, PTA; speech discrimination score, SDS; speech recognition threshold, SRT; acoustic-stapedial reflex, AR; tympanometry, TM).

Contouring will be performed on every MRI slice imported in the software.

Contouring will also be carried out for organs at risk, which are regionally defined to be the cochlea, brain stem, and uninvolved lower cranial nerves. The treatment plan, radiation dose, and number of sessions required will be tailored to patient characteristics, including lesion size, tumor proximity to organs at risk, and patient's hearing level by a certified radio-oncologist, a neurosurgeon, and a medical physicist. Next, the clinical care team will perform a final assessment of the treatment plan for isodose line tumor coverage, dose-volume histogram of organs at risk, and peak radiation dose foci. radiosurgery is performed by Leksell Gamma Knife® Icon™ device (Elekta, Sweden). Gamma knife radiosurgery with Leksell Gamma knife utilizes up to 192 radiation beams from cobalt-60 sources, which converge on the target foci with high precision. The radiosurgery device is equipped with a Cone Beam CT (CBCT) scanner to facilitate on-site stereotactic CT imaging prior to the start of the intervention. CBCT and the infrared camera system allow for the delivery of frameless gamma knife surgeries using mask-based immobilization. CBCT also allows for multiple session treatments and dose fractionation with maximal accuracy.

Sample Size and Statistical Analysis

In the absence of previous trials on the subject, sample size was calculated a priori using overall effect size guidelines [6]. Assuming statistically similar tumor volumes allocated to each group with a 1:1 ratio, 5% attrition rate, adjusting for and a baseline tumor volume of 12 cm^3 based on previous studies [3], the study sample size for each treatment arm was calculated to be 26, in order for the trial to have 80% power at a two-sided F-test analysis of covariance (ANCOVA) with a p-value of .05 to detect a clinically relevant major effect size (Numerator degree of freedom: 1, Cohen’s F: 0.40) [6]. Primary endpoint and secondary continuous outcomes will be assessed using independent t-test or ANCOVA as appropriate.

Differences in categorical data in baseline and symptoms in follow-up visits will be assessed using Pearson Chi-square test or Fisher-exact test or logistic regression for adjusting with baseline proportion if unbalanced. All analyses will be carried out using two-tailed statistics and an alpha of .050.

Data exclusion

This is a prospective randomized open blinded end-point (PROBE), single-center, non-inferiority, comparative study on patients with an established diagnosis of jugular paragangliomas. Due to the nature of the interventions, primary caregivers, physicians, data safety and monitoring committee, and patients are aware of the patient allocation. However, outcome assessors are selected from a group of licensed investigators blinded to randomization sequence and group assignment. Patients recruited into the study based on the inclusion criteria delineated further below are randomized into two equal study groups with 1:1 allocation ratio using 4-block permuted randomization. The first group would undergo 3-session fractionated SRS while the other group will be scheduled to receive SRS in a 5-session fractionated manner. The upcoming clinical trial will be registered in Iranian Registry of Clinical trials.

Patients were screened for eligibility and subsequently recruited after receiving informed consent based on the following inclusion and exclusion criteria:

Inclusion Criteria

- Male and female participants aged between 18 and 75 years.
- Individuals diagnosed with jugular paragangliomas with volumes exceeding 5cc.

Exclusion Criteria

- Individuals below 18 or above 75 years of age.

- Patient refusal to participate in the study.
- Previous radiotherapy for the lesion.
- Patients still recovering from acute high-grade toxicities of prior therapies.
- History of carcinoma within the last 5 years (excluding carcinoma in situ of the cervix, basal cell carcinoma, squamous cell carcinoma of the skin) requiring immediate treatment that interferes with the study therapy.
- Pregnant or lactating women.
- Concurrent participation in another clinical study or observation period of competing trials.
- MRI contraindication (e.g., cardiac pacemaker, implanted defibrillator, certain cardiac valve replacements, certain metal implants).
- Karnofsky Performance Score below 50.
- Simultaneous cytotoxic chemotherapy.

Data acquisition and follow-up

Demographics (Age, sex, body mass index, age at diagnosis), clinicopathological data (Fisch tumor grade, previous treatments, extent of resection, and cranial nerve examination) for each patient will be recorded and registered in the hospital data repository and anonymized electronic spreadsheets on the day of the intervention. Physical examination includes lower cranial nerve examination, facial sensory and motor neurological assessment, patient equilibrium, and additional examinations as indicated by patient presentation and findings. After revision and final approval of the treatment plan, a custom-fit three-point thermoplastic mask will be used for patients with multiple treatment sessions. Patients are asked to lie supine on the treatment bed with the thermoplastic mask affixing the patient's head. Subsequently, a stereotactic CT scan is taken by CBCT and merged with previous CT scans from earlier steps. Conformity of imaging data will be confirmed before

the start of the intervention. Fractionated radiosurgical sessions will be carried out on consecutive days without interruption. Data related to each intervention (Minimum and Maximum radiation dose in Gy, Average marginal dose, Isodose line, treatment isocenters, high-definition motion monitoring deviation threshold) will be documented for each patient.

Follow-up will be performed in 6-month intervals for patients undergoing radiosurgery in the affiliated neurosurgical clinics using office-based clinical examinations, T1, T1-contrast enhanced, T2, ToF, MRV sequences, and audiometry tests.

Evaluation Outcomes

The primary objective is to compare treatment efficacy between the study groups. The primary endpoint of the study is post-intervention tumor size, assessed by 6month and 1 year MRI sequences. Secondary outcomes include tumor status (reduction in size, no change, increase in size) compared to baseline imaging as well as percentage change of baseline tumor size, and presence of symptoms associated with jugular paragangliomas (Nausea/Vomiting, Tinnitus, Hearing loss, Dizziness, Vocal cord paralysis, Vertigo, Facial weakness/Paralysis, Hoarseness, Difficulty swallowing, and pain). The impact of dysphagia is evaluated using the translated version of dysphagia handicap index [7]. Perceived pain is evaluated using visual analogue scale scores for head and neck and referral pain associated with the primary lesion. The two former were considered as patient-reported outcomes. Incidence of safety outcomes and serious adverse outcomes (Hydrocephalus, Hemiparesis/Paralysis, Seizure, Mortality) will be also be documented and verified by the joint committee.

Withdrawal due to adverse events and reactions

A subject may be discontinued from the study if the subjects fall into one of the following criteria:

- Subject withdrawal
- Subjects without adherence to treatment regimen or non-compliant to the study procedures.
- Demonstrating any of the symptoms and conditions delineated in the safety outcomes.
- Lost to follow-up

All subjects will be free to withdraw from the study at any time during the trial. The withdrawn subjects will be included in the analysis in an intention-to-treat fashion.

Duration of the study

The study is completed after determining the endpoints of the last patients enrolled in the trial to fulfill sample size requirement. The maximum duration of the study for each subject will be 1 year.

Data will be obtained at baseline, 180 days, and 365 days after randomization from hospitalized patients. Participants will be followed-up for 1 year following inclusion and randomization.

All aspects of the study will be reviewed by institutional review board (IRB) at Tehran University of Medical Sciences prior to the start of the study. Written informed consent will be received from all participants prior to their enrollment.

Data Monitoring, Handling and Record Keeping

The primary and secondary investigators will contribute to data gathering during the study. The primary investigator oversees the validity of data gathering and

procedures performed by other investigators, and check for adherence to the trial protocol. Outcome assessment was performed by certified healthcare staff and physicians unaware of group assignment and not involved in treatment administration.

Hard copy of the documented baseline and outcome data will be retained until data entry. Deidentified data will be sent to the statisticians conducting the statistical analyses. Patient records will be kept after the end of the trial in hospital database.

Ethical considerations

Human subject ethics review approvals

The current work strongly adheres to the principles of the declaration of Helsinki. The finalized version of this protocol and the proposal written for conducting this trial will be subsequently evaluated by the IRB at Tehran University of Medical Sciences.

Informed consent

Each patient will be approached to obtain consent. Each individual will sign a form in which the trial, along with all procedures is fully described. Potential subjects would be fully informed that the study is voluntary and withdraw is completely possible in any stage of the trial without withholding standard of care or the fear that treatment may be biased in favor of the participating individuals.

Privacy and confidentiality

Each participating individual is ensured that their personal data will be removed prior to publication of the results and that they consent to authorizing access of their medical records and their results of trial procedures to trial investigators.

Results

Intervention

The enrollment process would proceed following the final approval of the current trial protocol by the Institutional review board of the affiliated university and prospective registration of the trial in the accredited Iranian registry of clinical trials (IRCT). The estimated starting date of the enrollment process is June 2024 and the duration of the trial is 2 years from the start of enrollment. The treatment plan for each patient will be developed using the GammaPlan software by the study physicist, employing isocentric rays with diameters of 4, 8, and 16 millimeters. The treatment approach is meticulously crafted to ensure that the therapeutic isodose envelops the entire contoured area, and the dose coverage attains a minimum of 95% (preferably 97%). Fractionated and cumulative therapeutic doses will be tailored based on tumor size, location, and proximity to organs at risk. Patients allocated to the 3-session fractionated gamma knife radiosurgery group will receive doses ranging from 18-21 Gy (6 to 7 Gy in each session), while those assigned to the 5-session group will receive doses within the range of 20-25 Gy. Through translocation and assigning appropriate weights to the utilized rays, the study physicist will endeavor to enhance the coverage of the therapeutic dose, diminish doses received by organs at risk, and optimize the selectivity, conformity, and gradient index of the treatment plan. Reaching this goal would require multiple rays and blocking a portion of each ray. In the majority of cases, treatment plan will proceed using 50% isodoses. In such instances, the doses received by the tumor center would be twice that of what the tumor margin would receive. During the formulation of the treatment plan, the treatment duration in each session will not be employed as the decisive factor. Instead, among multiple potential plans, those with a lower treatment duration will be selected if other

factors and characteristics are comparable. Dosimetry will be conducted using the Tissue-Maximum Ratio (TMR10) algorithm and 1-2mm grids, contingent on the lesion size. Upon completion of the treatment plan design, the primary neurosurgeon and radio-oncologist assigned to the patient will validate the mentioned values and recalculate the final doses received by organs at risk. Endeavors will be made to maintain the Gradient Index below 3, the Conformity Index below 1.5-2, and achieve selectivity as close as possible to 1 [8]. These terms have been explained as below.

$$Coverage = \frac{V(PIV \cap TV)}{V(TV)}$$

$$Gradient\ Index = \frac{V\left(PIV_{\frac{iso}{2}}\right)}{V(PIV_{iso})}$$

$$Selectivity = \frac{V(PIV \cup TV)}{V(PIV)}$$

Metrics employed to evaluate the dose distribution in radiosurgery planning. PIV: prescription isodose volume, TV: Target volume

Discussion

As the primary objective, the current investigation aims to conduct a comparative analysis of post-intervention tumor size between three sessions and five sessions of fractionated gamma knife radiosurgery in the treatment of Jugular paragangliomas. The findings of this trial will provide critical insight and evidence-based alternative treatment options for jugular paragangliomas by optimizing therapeutic outcomes while minimizing treatment burdens on patients. The results will be instrumental in refining current guidelines for radiosurgical management, enabling more precise

tailoring of treatment plans based on tumor volume response and patient-specific characteristics.

Numerous studies in the literature have advocated for the utilization of radiosurgery as a recommended modality in the management of Jugular paragangliomas due to its ability to effectively control tumor progression and alleviate pre-intervention tumor-related symptoms. Although, Recent trials have reported an overall tumor control rate ranging from 95 to 100 percent, contingent upon the specific tumor size and the duration of subsequent observations [9-12]. Apparently, fractionated gamma knife SRS attenuated the impact of radiation beams on the surrounding tissues, while also providing intervals between each session to facilitate the restoration of normal tissues. However, it is crucial to consider the quality of life as a significant component throughout the treatment process for all stages of the disease. Therefore it is a reasonable conclusion that the potential adverse symptoms are diminished via reduction of radiation exposure to organs at risk [5].

Although the study institution functions as a referral center, the single-center design of this trial may introduce selection bias that must be carefully considered when interpreting the results, possibly limiting the generalizability of the findings. However, given the rarity of the condition and the limited adoption of stereotactic radiosurgery (SRS) in this region, the single-center approach is justified. Concentrating the trial at a single institution allows for specialized expertise, consistent methodology, and comprehensive data collection. These factors enhance the study's validity and help generate crucial insights that will guide treatment practices in regions with similar challenges.

Conclusions

Based on numerous research investigations, there exists an insufficient amount of

information to establish a comparison between various dosage fractionations of gamma knife radiosurgery. Consequently, drawing from this body of knowledge, future studies could utilize the current findings to investigate alternate dosing and fractionation studies to establish a complete guideline for dose-response and fractionation strategies for radiosurgical operations.

Abbreviations

ANCOVA: analysis of covariance
CBCT: Cone Beam CT
CT: computed tomography
Gy: Gray
JP: Jugular paraganglioma
MRI: Magnetic resonance imaging
MRV: magnetic resonance venography
PIV: Prescription isodose volume
PROBE: prospective randomized open blinded end-point
SRS: Stereotactic Radiosurgery
TMR10: Tissue-Maximum Ratio
ToF: time of flight
TV: Target volume

Statements and Declarations

Ethics approval and consent to participate

All experimental protocols to be performed in the upcoming trial are in line with the declaration of Helsinki and was approved by Tehran University of Medical Sciences institutional ethics committee. Informed consent to participate will be obtained from patients eligible for the trial.

Consent for publication

Not applicable.

Availability of data and materials

The data generated in the upcoming trial will be available on reasonable request from the corresponding author.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contributions

ES and AL will be the primary investigators in the trial and conceptualized the trial. MS, MB, MAB, and HN will be secondary physicians participating in patient screening and data curation. KKY and MS will be supervising the trial. FM, ABB, and SA have contributed to writing the draft for the current work and revising the protocol. SA will act as the primary statistician for the upcoming trial.

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References

1. Fernández-de Thomas, R.J. and O. De Jesus, *Glomus jugulare*. 2020.
2. Fernández-de Thomas, R.J. and O. De Jesus, *Glomus Jugulare*, in *StatPearls*. 2023, StatPearls Publishing

3. Ong, V., et al., *Stereotactic radiosurgery for glomus jugulare tumors: systematic review*

and meta-analysis. World Neurosurgery, 2022. **162**: p. e49-e57.
4. Kalhoro, A. and A.S.M. Hashim, *Glomus jugulare tumors treatment by gamma knife radiosurgery: A single center study.* Pak J Med Sci, 2023. **39**(1): p. 46-49.
5. Tripathi, M., et al., *Safety and efficacy of primary multisession dose fractionated gamma knife radiosurgery for jugular paragangliomas.* World neurosurgery, 2019. **131**: p. e136-e148.
6. Cohen, J., *Statistical power analysis for the behavioral sciences*. 2013: Routledge.
7. Silbergleit, A.K., et al., *The dysphagia handicap index: development and validation.* Dysphagia, 2012. **27**: p. 46-52.
8. Chagas Saraiva, C.W., et al., *Gamma Knife radiosurgery for vestibular schwannomas: Evaluation of planning using the sphericity degree of the target volume.* PLoS One, 2020. **15**(1): p. e0225638.
9. Guss, Z.D., et al., *Radiosurgery of glomus jugulare tumors: a meta-analysis.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e497-502.
10. Hafez, R.F., M.S. Morgan, and O.M. Fahmy, *An intermediate term benefits and complications of gamma knife surgery in management of glomus jugulare tumor.* World J Surg Oncol, 2016. **14**(1): p. 36.
11. Ibrahim, R., et al., *Gamma Knife radiosurgery for glomus jugulare tumors: a single-center series of 75 cases.* J Neurosurg, 2017. **126**(5): p. 1488-1497.
12. Tripathi, M., et al., *Safety and Efficacy of Primary Multisession Dose Fractionated Gamma Knife Radiosurgery for Jugular Paragangliomas.* World Neurosurg, 2019. **131**: p. e136-e148.

Supplementary Files

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CONSORT (or other) checklists

Cover letter.
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