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Exploring Radiation Therapy for Head and Neck Paragangliomas: Insights from a Tertiary Care Hospital

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Abstract

Aims and Objectives: The aim of this study was to determine the epidemiological parameters, including age and sex distribution, clinical presentation, tumour classification and role of radiation therapy in the management of head and neck Paragangliomas.

Materials and Methods: This was a retrospective study of 15 patients treated for head and neck Paragangliomas in the Department of Radiation Oncology Government Medical College, Srinagar between January 2021 and April 2023.

Results: The median age of the study participants was 50 years, ranging from 26 to 70. Among the patients, there were 10 females and 5 males, resulting in a sex ratio of 2:1. Tinnitus was the most frequent symptom, observed in 64% of cases, followed by Vertigo (28%), Headache (21%), and hearing loss (21%). 86.7% of Paragangliomas were benign while 13.3% were malignant. All patients (15 patients) underwent radiation therapy, which was used exclusively in 12 (80%) patients and as an additional treatment following surgical resection in 3 (20%) patients. The median radiation dose administered was 50Gy, with a range of 25-54, and it was delivered through Image Guided Radiotherapy (VMAT and IMRT). There were no severe treatment related complications. After a median follow-up period of 18 months, ranging from 6 to 28, all patients achieved local control, defined as radiological stability or regression, and there were no reported deaths.

Conclusion: In conclusion, this study demonstrated the effectiveness of radiation therapy in managing a diverse group of patients with varying symptoms. Most patients achieved local control with minimal complications during 18-month follow-up, underscoring the treatment's success.

Keywords: Paraganglioma, Head and Neck, Radiotherapy.

Introduction

Paragangliomas or chemodectomas are uncommon tumors that develop from the paraganglia, which are clusters of neuroendocrine cells positioned along the blood vessels and nerves in the head, neck, and spine. Typically benign, these tumors grow slowly, causing symptoms as they put pressure on nearby structures [1].

Head and neck Paragangliomas (HNPGls) have an incidence rate ranging from 1 in

30,000 to 100,000. They are most commonly found in the carotid body (known as carotid body Paragangliomas), followed by the jugular bulb, the vagus nerve (CN X), and the tympanic branch of the glossopharynx (CN IX) or cervical sympathetic chain, in decreasing order of occurrence [2].

In some cases (10%), a second Paraganglioma can appear together, and about 85% of those with a genetic predisposition may have multiple growths. The most common simultaneous occurrence is a second carotid body tumor (20% of such tumors). Treating patients with additional growths on the opposite or same side poses challenges due to potential nerve and blood pressure complications. Monitoring with imaging tests like MRI or PET scans is recommended for multiple or sequential tumors [29-31].

Paragangliomas, typically non-malignant, can become metastatic, particularly in sporadic cases and certain genetic mutations like SDHB. Rates of malignancy vary by site, with orbital and laryngeal paragangliomas having the highest rate at 25%. Diagnosing malignancy relies on finding tumors in lymph nodes or distant spread. Treating malignant cases involves surgery and radiotherapy for local control, but recurrence can occur for up to two decades. Survival rates range from 50% to 80% for nodal disease and up to 11% for distant spread over 5 years [41].

Treatment options for HNPGls include observation, surgery, external beam radiation therapy (EBRT). Primary radiotherapy may be delivered by conventional fractionation EBRT (45Gy in 5 weeks), Stereotactic Radiosurgery (SRS) with doses ranging from 12-15Gy in single fraction or hypofractionated stereotactic radiation therapy (SRT) with doses ranging from 21-25Gy in 3-5 fractions. The primary and definitive treatment involves complete surgical removal. Radiotherapy becomes necessary as an additional treatment after partial resection or as the sole option for unresectable tumors or patients who are not suitable for surgery [3].

Traditionally, radiotherapy was offered to those unable to undergo surgery due to various reasons. Concerns about its effectiveness exist since lesions rarely regress completely post-treatment. Yet, evidence supports moderate radiation doses for long-term efficacy in preventing tumor progression and preserving cranial nerve function. It's now a primary treatment for mostly benign tumors, commonly used for certain skull-base and vagal tumors. Successful treatment means stability or partial regression, determined through regular imaging. Different radiotherapy methods like conventional EBRT, stereotactic radiosurgery, or hypofractionated stereotactic radiotherapy show excellent local control rates. The choice depends on tumor size and location. Stereotactic approaches suit smaller intracranial tumors, while larger or extracranial spread tumors benefit from EBRT. Radiation impact on paragangliomas includes vascular changes, necrotic tissue, and fibrosis, preventing tumor growth and affecting cell reproduction [41].

While there are documented cases in the literature demonstrating excellent local control of Paragangliomas treated with RT, there have been limited series of cases reported in our practice setting [4] [5]. This study presents the therapeutic outcomes gathered from 3 years of managing head and neck Paragangliomas at our Institution.

Materials and Methods

This study retrospectively examined 15 patients who underwent treatment for HNPGls at the Department of Radiation Oncology, GMC Srinagar, J&K, spanning from January 2021 to April 2023. Data were retrieved from the patients' medical records. Patients eligible for inclusion exhibited a strong clinical and imaging suspicion of Paraganglioma without undergoing surgery or having histologically confirmed Paraganglioma. Among the

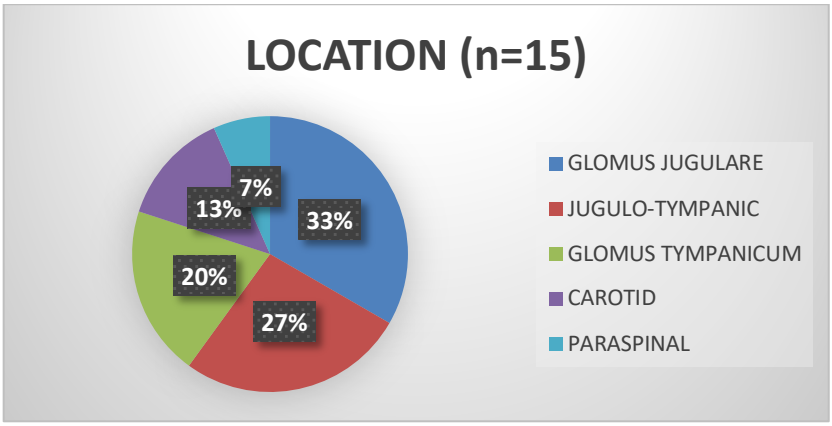
identified cases, those who underwent radiotherapy were incorporated into our investigation. Subsequently, we gathered information concerning patient demographics, tumor characteristics, clinical and paraclinical indicators, symptoms, treatments administered, and follow-up details.

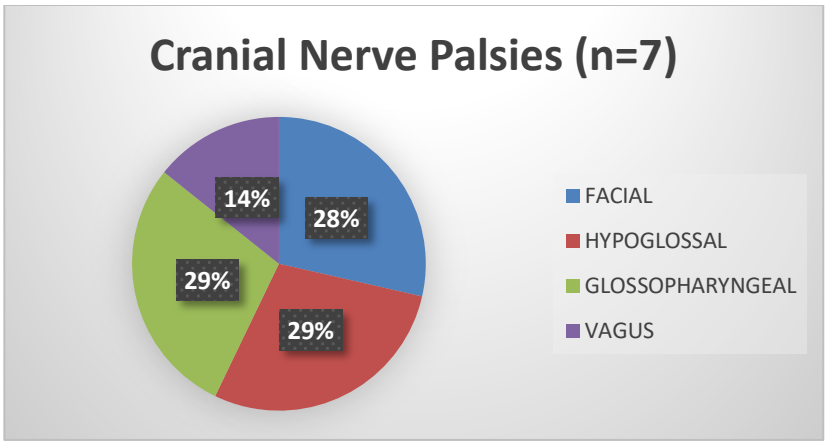
Results

The median age of the cohort was 50 years (range: 26 - 70). Among the participants, there were 10 females and 5 males, resulting in a sex ratio of 2:1. Tinnitus emerged as the most prevalent symptom (64%), followed by vertigo (28%), headache (21%), hearing loss (21%), and neck swelling (14%). The Paraganglioma was predominantly located in the jugular bulb (33.3%), glomus Tympanicum (20%), Jugulo-tympanic (26.7%), carotid (13.3%) and cervical paraspinal region (6.7%). All patients were having benign Paragangliomas. 60% of Paragangliomas were present on left side while 40% were present on right side. Cranial nerve palsy was present in 6 (40%) patients which included 2 facial nerve (VII), 1 vagus nerve (X), 2 glossopharyngeal nerve (IX) and 2 hypoglossal nerve (XII) palsy. All 15 patients were non-secretory type. Tumor sizes varied between 1.2 to 7.7 cm. Histological confirmation was available in 5 (33.3%) of cases. Post-operative biopsy was present in 3 patients, FNAC in one and Tru-cut biopsy in one patient. Using the FISCH staging system, 8 patients (53.3%) were classified as Class C, while 3 patients (21%) fell into Class D (refer to Table 1).

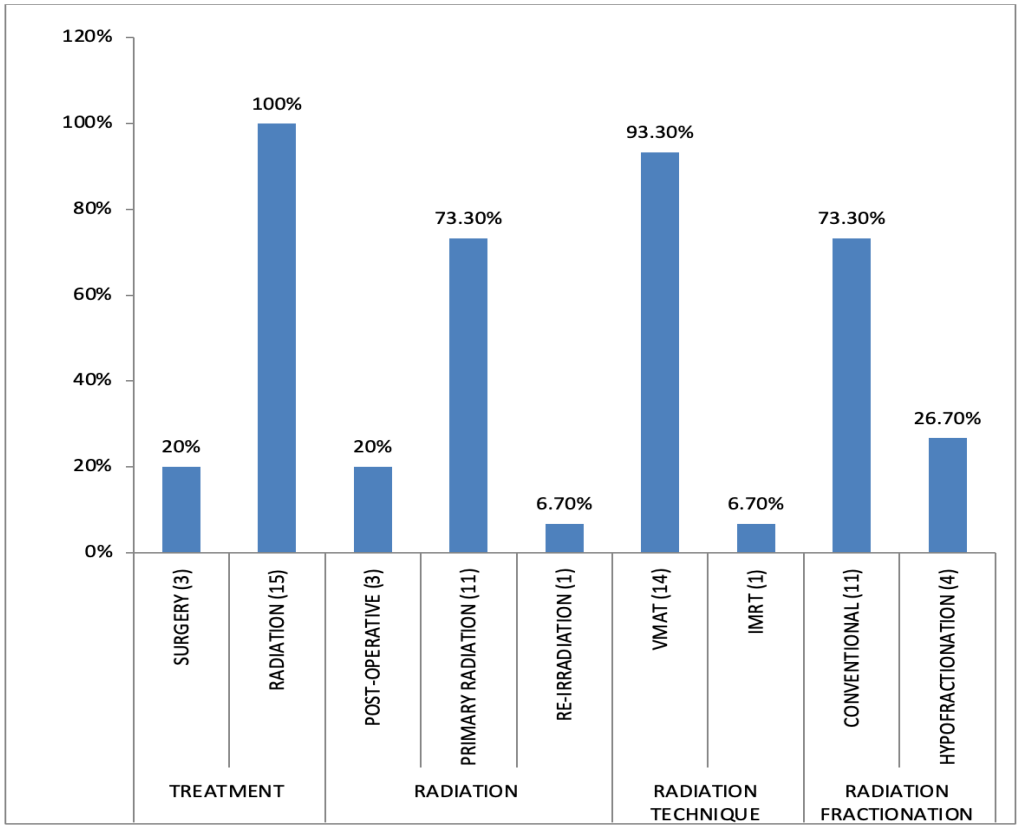
Table 1: patient and tumor characteristics

AGE		**50Years (26-70)**
GENDER	Male (5) Female (10)	33.3% 66.7%
SYMPTOMS	Tinnitus Vertigo Headache Hearing Loss Neck Swelling	64% 28% 21% 21% 14%
NATURE	Benign (13) Malignant (2)	86.7% 13.3%
Laterality	Right side (6) Left side (9)	40% 60%
SIZE		1.2cm-7.7cm
FISCH class	Class C Class D	53.3% 21%





Surgery was performed in 3 patients. All 15 patients underwent radiation therapy, with 3 patients receiving adjuvant treatment due to residual disease post-surgery. Primary radiotherapy was delivered in 11 patients while 1 patient was re-irradiated due to progressive symptoms and size of lesion after previous primary radiotherapy 2 years ago. The median radiotherapy dose was 50 Gy (range: 25 - 54). Radiation was delivered by Image guided conformal Radiotherapy in all 15 cases (VMAT in 14 patients and IMRT in one). 11 (73.3%) patients were treated with conventional fractionation with doses ranging from 45-54Gy in 25-30 fractions. 4 (26.7%) patients received hypofractionated SRT with doses ranging from 25-35Gy in 5-8 fractions. Symptom improvement was observed in 14 patients while 1 patient was asymptomatic at presentation and was diagnosed during evaluation of another primary malignancy.



Regarding acute complications, 3 patients experienced grade I-II mucositis, while 2 patients encountered grade I dermatitis. After a median follow-up duration of 18 months (range: 6 - 28 months), all 15 patients achieved local control, defined as either stability or radiological regression, and there were no recorded deaths.

Discussion

We present findings based on a 34-month study conducted at a single center, involving the treatment of 15 patients diagnosed with HNPGls. The median age at diagnosis was 50 years, consistent with existing literature where the age span varied widely. For instance, Kollert et al. reported a median age of 49 years (ranging from 26 to 75), while Papaspyrou noted 52 years (ranging from 10 to 85) [6] [7]. However, occurrences of PGls in children are exceptionally rare [8]. Our series, like several studies, displayed a female predominance, aligning with observations where tumor location seemed correlated with gender distribution. Carotid Paragangliomas tended to affect males, whereas jugular, temporal, and vagal Paragangliomas were more commonly found in women [9, 10, 11].

Head and neck Paragangliomas (HNPG) predominantly affect females, occurring at an estimated rate of 1 in 30,000–100,000. They most commonly originate from various sites, with the carotid body (CBP), jugular bulb (IJP), vagus nerve (VP) (5%), the tympanic branch of the glossopharyngeal nerve or auricular branch of the vagus nerve (TP), and the cervical sympathetic chain (SCP) being the primary sources in descending order of occurrence [12, 13, 14]. In our study, 33.3% were glomus Jugulare, 20% were glomus Tympanicum, 26.7% were Jugulo-tympanic, 13.3% were carotid, and 6.7% were cervical paraspinal Paragangliomas. Paragangliomas are rarely malignant, representing a small subset of extra-adrenal Paragangliomas with a propensity for regional lymph-node and distant metastatic disease, primarily to bone, the lungs, and liver [29-31]. The rate of malignancy depends on the site of origin. Although rare, orbital and laryngeal Paragangliomas have a 25% rate of malignancy, which is the highest rate of any Paraganglioma. By comparison, the rate of malignancy for vagal Paragangliomas is between 16% and 19%, between 5% and 6% for Jugulo-tympanic Paragangliomas, and between 3% and 4% for carotid body tumors [38]. No histological criteria exist to diagnose malignancy in primary tumors. The health care professional can make the diagnosis only if malignancy is confirmed by the presence of a tumor in the lymph nodes or the disease has metastatically spread to distant sites [29-31]. In our study, all 15 patients were having benign Paragangliomas. Dysfunction of the cranial nerve may be indicative of presence of large tumors extending into the jugular foramen. Typically, temporal bone Paragangliomas are located in the jugular fossa, and symptoms may involve early functional impairment of cranial nerves IX, X, XI within the jugular foramen, and XII as it exits the hypoglossal canal [29-31]. In our study, Cranial nerve palsy was present in 6 (40%) patients which included 2 facial nerve (VII), 1 vagus nerve (X), 2 glossopharyngeal nerve (IX) and 2 hypoglossal nerve (XII) palsy. The Fisch and Mattox classification, frequently utilized for HNPGls, categorized 53.3% of our patients as class C and 21% as class D, both representing advanced tumor stages. Extra-adrenal Paragangliomas lack methyltransferase, a requirement for converting norepinephrine to epinephrine; the metabolic breakdown of catecholamines to metanephrine (from epinephrine) and nor-metanephrine (from nor-epinephrine) as well as vanillyl-mandelic acid (VMA) can be detected in urine. Thus, appropriate urine and serum analysis can be used to detect actively secreting Paragangliomas [29-31]. In our study, all 15 patients were non-functional (non-secretory). Paragangliomas are more common on the left

side and same is found in our study with 60% on left side while 40% are found on right side.

Management of Paragangliomas varies based on several factors such as tumor size, extent, initial treatment, patient's age, overall health, and neurological condition [16]. Surgery remains the primary option for complete removal, aiming for total resection. However, due to their vascularity and involvement of critical structures, total removal may pose significant risks. For larger lesions (FISCH class C or D), surgical resection might necessitate cranial nerve resections, making radiotherapy a better alternative. In our series, 20% of patients in whom tympanic cavity was involved underwent partial surgical resection before salvage radiotherapy. Some studies suggest that primary radiotherapy could yield better results than postoperative radiation following incomplete tumor resection [10].

Primary radiotherapy may be delivered with conventional external beam radiotherapy (EBRT), stereotactic radiosurgery, or hypofractionated stereotactic radiotherapy. All of these approaches have excellent rates of local control and outcomes [29-31]. Typically, doses of 45 Gy in 5 weeks are given with conventional EBRT, 12 to 15 Gy with stereotactic radiosurgery, and 21 Gy for 3 fractions or 25 Gy for 5 fractions with hypofractionated stereotactic radiotherapy [29-31]. Patients whose intracranial tumors measure less than 3 cm are the best candidates for stereotactic approaches, whereas those whose tumors are larger or have a component of extracranial spread are best suited for EBRT [29-31]. The ablative nature of stereotactic radiosurgery can cause a small increase or exacerbation in the rate of cranial neuropathy, and, thus, a more fractionated approach with stereotactic radiotherapy or conventional EBRT may be considered in those whose baseline cranial nerve function is excellent [29-31].

All 15 patients in our study received external beam radiation therapy, with various image guided techniques including Volumetric Arc Therapy (VMAT) and Intensity Modulated Radiotherapy (IMRT). Radiation was delivered using conventional fractionation in 11(73.3%) patients and hypofractionated SRT in 4(26.7%) patients. Studies have shown that tolerated radiation doses range between 32 to 60 Gy in 16 to 30 fractions with favourable outcomes with doses exceeding 40 Gy and even better results with prescribed doses of 45 - 60 Gy in 1.43 - 2 Gy/fraction [19]. In our study, radiation dose ranged between 45 to 54 Gy @ 1.8Gy per fraction in conventional fractionation and 25 to 35 Gy @ 4-5Gy per fraction in hypofractionated schedules.

Most recurrences are amenable to radiotherapy. Multiple authors have reported local control rates of 88 to 96% in patients treated with radiotherapy after failed surgery, combination radiation/surgery, or radiotherapy alone. These 24 studies are well summarized in a review article by Carrasco and Rosenman [40]. Of the 582 patients in this meta-analysis, an overall local control salvage rate of 95% was noted. Radiotherapy regimens varied, but most patients in the more recent studies received full-dose (45 Gy) radiotherapy without serious sequelae. However, when retreatment radiotherapy is preformed, great care must be exercised to respect the normal tissue tolerances of critical structures, especially the temporal lobe of the brain and cranial nerves. In our study, 1 patient was re-irradiated with full dose of radiotherapy (45Gy) after progression of symptoms and size of the lesion almost after 2 years of primary radiotherapy.

Long-term tumor stabilization or partial regression is the objective with radiotherapy, rather than complete remission [27] [28]. Results of the radiographic follow-up of patients after EBRT demonstrate stability in tumor size or modest tumor regression [32, 33, 34]. Mukherji et al [35] reported on 17 patients

with 18 Paragangliomas treated with definitive radiotherapy who underwent pre-treatment and post-treatment imaging using CT or MRI. A total of 61% showed a decrease in tumor size, with an average reduction of 23% (range, 8%–45%) at a median follow-up of 2.5 years. Post-radiotherapy findings on MRI included reduction in flow voids, decreased heterogeneous enhancement, and a reduced T2 signal [35]. Other studies have demonstrated tumor regression in 57% to 73% of patients followed by CT [36, 37]. Thus, Paragangliomas will show modest radiographic change or stable tumor in the majority of cases. In our study, after an 18-month median follow-up, all 15 patients achieved radiological local control.

Rates of morbidity following radiotherapy vary according to the radiation technique and treatment site. Common toxicities related to radiotherapy include mucositis, fatigue, otitis, dermatitis, nausea, xerostomia, epilation, skin dryness, fibrosis, and cerumen build-up {29-31]. In our study, 3 patients experienced grade I-II mucositis, while 2 patients encountered grade I dermatitis which was easily manageable. Similar retrospective studies have reported comparable local control and overall survival rates, demonstrating the efficacy of RT and SRT with minimal treatment-related complications [27] [11] [16]. However, due to the rarity of Paragangliomas and the short follow-up duration, limitations exist in fully capturing late radiotherapy-induced toxicities. Nonetheless, our study, alongside others, underscores the significance of RT and SRT in the comprehensive treatment approach for these tumors.

Conclusion

Paragangliomas, uncommon tumors found in the head and neck, exhibit slow growth and the potential to spread to the vascular and bony structures at the base of the skull. The primary treatment is complete surgical removal while radiotherapy is the treatment of choice for Paragangliomas which present in anatomic areas with difficult surgical access, involve critical structures or present over a large geographic area. Newer techniques, such as stereotactic radiosurgery have improved the intracranial local control of this disease while averting operative morbidity and mortality. Considering the reduction in morbidity with radiotherapy, we believe that primary irradiation should be considered the standard of care in all but the most easily accessible tumors. The fractionated dose delivered should be around 45 Gy. Stereotactic radiotherapeutic doses should not exceed 18 Gy with 12 Gy being the preferred single fraction dose. Retreatment radiation is safe and effective for both surgical and radiotherapeutic failures.

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