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Linear Accelerator Based External Beam Radiotherapy in Glomus Jugulare Tumour: A Retrospective Review from a Tertiary Cancer Hospital in Kenya

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Abstract

Objective: Tumours originating from jugular bulb, carotid bifurcation, Vagus nerve are collectively called Paragangliomas. They are slow growing, essentially benign tumours, but can be detrimental if untreated. There is limited evidence on the effectiveness of fractionated radiotherapy in the management ofs Glomus jugulare tumours. The aim of this study is to determine the efficacy of Linear accelerator based fractionated external beam radiotherapy on unilateral inoperable Glomus jugulare paragangliomas. Method: This is a retrospective analysis of all the 12 cases of inoperable, unilateral Glomus jugulare tumours treated during the period 2011-2016 at a tertiary cancer centre in Kenya. Minimum follow up duration was 3 years. Patient characteristics, disease staging, immediate complications and therapeutic efficacy were analysed from the case files. Results: The 12 patients diagnosed with inoperable Glomus jugulare tumours reported in this period were treated with external beam radiotherapy to a tumour dose of 54 Gy in 30 fractions over a period of 6 weeks using IMRT technique in 6 MV Linear accelerator. 2/3rd of the patients were females in 5th and 6th decade of life. Onset of first symptom to initiation of treatment was found to be 1.7 years. Headache, earache, and tinnitus were the main complaints. No major side effects were recorded during therapy. Mean length of the tumour in its maximum dimension at the time of diagnosis was 4.5 cm. At the end of one-year post therapy, a mean reduction of 6.5 mm in the tumour length was observed, (Range: 0 - 15 mm). Tumour size remained static for a year and thereafter a slow growth pattern of 1mm per year was observed. Conclusion: Fractionated external beam radiotherapy is an effective and non-invasive treatment for advanced, inoperable Glomus

jugulare paragangliomas. Clinical stability through tumour control was observed. Though newer radiation techniques like Cyberknife, Proton therapy offer better tumour control, conventional external beam radiotherapy is an effective tool in disease containment in resource limited countries.

Keywords

Glomus Jugulare, Paragangliomas, External Beam Radiotherapy

1. Introduction

Tumours arising from the paraganglia of the chemoreceptor system, otherwise known as Paraganglioma or chemodectoma are the most common neurological neoplasms after acoustic neuroma. These paragangliomas are considered sporadic if they occur in patients who do not have any family history of genetic syndrome. But recent studies suggest the existence of 4 genetic paraganglioma syndrome, all with autosomal dominant transmission in sporadic paragangliomas [1]. Hence genetic screening is gaining prominence in identifying potential candidates for paragangliomas. Glomus jugulare, the most common jugular fossa tumour, is a paraganglioma of the head and neck that is confined to jugular fossa. These tumours are rare-one in one million [2]. They have a female preponderance and occur mostly in the 5th or 6th decade of life [3] [4]. They have rich neural supply from Glossopharyngeal nerve as well [5]. These highly vascular tumours are histologically benign and non-secreting paragangliomas [6] [7] [8] [9]. Malignant variations occur in approximately 3% of cases [10]. These tumours are locally advancing, they may invade surrounding structures such as the middle ear, jugular vein, clivus, internal carotid artery, cavernous sinus, and cranial nerves [11]. Such local advancement of the growth may become life threatening. Symptoms of Glomus jugulare tumours are usually caused by local invasion of adjacent structures or mass effect. Patients with Glomus jugulare tumours exhibit hearing loss, tinnitus, headache, dizziness [12]. The interval between the first symptom and diagnosis is 4 to 6 years [13].

Diagnosis of paraganglioma is done with imaging. Computerised tomography scan (CT) and magnetic resonance imaging (MRI) are widely used as the initial evaluation methods. CT has a lower sensitivity [14], but accurately defines possible bone invasion. Paragangliomas show a characteristic "salt-and-pepper" pattern and intense post-contrast enhancement in MRI. MR Angiography which can define the vascular anatomy preoperatively to ensure safe preparation for a vascular reconstructive surgery is a particularly important method in diagnosis. Recently, PET scan is also extensively used to stage the disease. It can detect small and metastatic lesions, if any [1].

There is no consensus in the treatment of these tumours due to rarity of the cases. The aim of treatment is broadly divided as curative and palliative. Many researchers believe that the treatment modality for Glomus jugulare tumours

should be dictated by the size of the tumour [13]. The only curative treatment available is surgery, and the palliative treatment may include radiotherapy or wait and watch protocol [15].

This study aims to find out the efficacy of Linear accelerator based external beam radiotherapy in the management of advanced, inoperable, unilateral Glomus jugulare paraganglioma in a tertiary cancer centre in Kenya. Complications of therapy also were explored.

2. Patients and Method

All 12 patients diagnosed with unilateral, monocentric, inoperable Glomus jugulare tumours treated with external beam radiotherapy between 2011 to 2016 were included in the study. Patients had no family history of Paraganglioma. Staging was done using Fisch [16] classification (**Table 1**).

Total delivered dose in every case was 54 Gy in 30 fractions, over a period of 6 weeks using a 6 MV linear accelerator. IMRT technique was used to deliver radiotherapy. They were periodically followed up at the Department of therapeutic radiology of Cancer Care Kenya, Nairobi. Personal data, clinical history, findings of physical examination, response to therapy, acute and late side effects of therapy of the patients were analysed. Minimum follow up duration was 3 years. Radiological response was assessed with MRI evaluation. Follow up schedule was: 3 monthly reviews for the first year, six monthly reviews for next 2 years, and annual reviews afterwards. At every appointment, patients were thoroughly examined for symptoms and underwent MRI evaluation at prescribed intervals. The findings were documented in the individual case files. Simple arithmetic calculation to find out the measures of central tendency was employed for statistical analysis.

3. Results

The following tables (**Tables 2-5**) summarise the results of the study.

In our study group, 50% were in 5^{th} decade and 25% were in 6^{th} decade. Paragangliomas spare the young. There was female preponderance for the disease. 75% were women. Tumour is indolent in nature. Patients seek medical attention at a late stage as they do not have any major medical complaints for nearly a year. Interval between the first recognised symptom and diagnosis of the disease was 1.7 years. Longest follow up duration for this small series of cases was 8 years. No mortality observed in the series.

Table 1. Fisch classification of Glomus Jugulare tumours.

A	Limited to middle ear cleft
B	Limited to tympanomastoid area
C	Involving the infralabyrinthine compartment and petrous apex of temporal bone
D1	Intracranial extension <2 cm in greatest dimension
D2	Intracranial extension > 2 cm in greatest dimension

Table 2. Patient characteristics.

Sl. No.	Age	Sex	Symptom Duration (years)	Follow up (years)
1	32	F	3	8
2	47	F	1	7
3	58	M	1	5
4	60	F	2.5	6
5	56	F	1	6
6	52	F	1	5
7	63	F	2	4
8	58	M	3	4
9	67	M	2	4
10	45	F	2	3
11	50	F	1	3
12	54	F	1	3
n:12	Median:52.6	M:F-1:3	Mean-1.7	Mean-4.83

Table 3. Common signs and symptoms.

Signs and symptoms	n	Percentage
Defective hearing	10	83
Ear pain	12	100
Ear discharge	8	66
Tinnitus	11	92
Vertigo	7	58
Lower cranial nerve palsy	4	33
Headache	12	100

Table 4. Common acute side effects of radiotherapy.

Side effect	n	Percentage
Dermatitis	4	33
Oral mucositis	8	66
Mastoiditis	6	50
Otitis	9	75
Xerostomia	4	33
Hearing defect	10	83

All patients had pain in the affected ear and headache. 83% had hearing defects. Symptoms or signs that demand immediate medical attention were rare. Facial palsy or defective speech was not commonly seen. The neoplasm usually originates in the region of jugular bulb, hence lower cranial nerve involvement is likely to happen, but in our series, they were infrequent.

Table 5. Tumour stage and treatment response.

Sl. No.	Fisch stage	Size at therapy beginning (mm)	Size at 3-month post therapy (mm)	Size at 1-year post therapy (mm)	Size at 3-year post therapy (mm)
1	D2	59	44	40	52
2	B	46	32	30	36
3	B	25	25	32	35
4	B	21	17	18	21
5	D1	35	30	30	33
6	A	28	27	20	16
7	D2	70	66	64	60
8	D1	53	35	44	47
9	B	37	32	30	32
10	D1	55	55	52	54
11	C	49	43	40	40
12	D1	62	61	62	64
n:12	--	Mean 45	Mean 39	Mean 38.5	Mean 41

Literature related to Linear accelerator based external beam radiotherapy as a single modality treatment for Glomus jugulare is relatively sparse. The most common side effect observed was hearing defect. Patients present with hearing defect and the symptom worsened after radical radiotherapy. Defective hearing did not lead to deafness. Fractionated radiotherapy caused protracted otitis in 2/3rd of the patients.

Patients in all Fisch stages were in the study, however, majority were in Stage D. The mean size of the tumour in its greatest dimension at the time of diagnosis was 45 mm. 93% of the patients, treated with external beam radiotherapy, had reduction in tumour size. Average reduction in size after 3 months post radiotherapy was observed as 6 mm (range: 0 - 15 mm). External beam radiotherapy is not a curative treatment in inoperable giant Glomus jugulare tumours. Tumour control and clinical stability was achieved in all patients.

4. Discussion

Glomus Jugulare is a paraganglioma originating from paraganglia—small groups of neuroendocrine cells arising from the autonomic nervous system ganglia. Tumours arising from the parasympathetic paraganglia are usually non-chromaffin and rarely secrete catecholamines, when compared with their sympathetic counterparts [17]. Head-and-neck paragangliomas are rare tumours, representing 0.012% of a large oncological surgical series [18]. The classical main sites of origin are as follows: carotid bodies at the bifurcation of the common carotid artery; jugular paraganglia close to the jugular bulb and tympanic paraganglia in the middle ear—usually considered together and vagal paraganglia along the Va-

gus nerve [13]. The disease usually affects the 5th or 6th decade of life [3] [4]. Management of Glomus tumours is still controversial. There is no uniform consensus on the therapy. Surgery, External beam radiotherapy, ablative procedures are all used with varying results.

Surgical excision of Glomus jugulare tumours are often difficult and are considered only when they are symptomatic due to brain stem compression or raised intracranial pressure [19]. For Glomus jugulare tumours, surgery is the treatment of choice in younger patients with smaller lesions and significant lower cranial nerve dysfunction [20] [21], because further functional deficits can be aborted. Large tumours with intracranial extension, involvement of the foramen magnum, or vascular encasement of major vessels pose major challenge to surgery [22]. Local tumour control following surgery vary from 80% to 90% [8] [23] [24]. In addition, excision can be associated with significant patient morbidity and death. In such cases, pre-operative radiotherapy offers promising outcome. An en-bloc dissection may be feasible if preoperative radiotherapy has been given for larger tumours. The stromal fibrosis enables the surgeon to remove the tumour without fragmentation and thus diminishes the ultimate intraoperative blood loss [25].

Although some investigators opine that these tumours are radioresistant, fractionated external beam radiotherapy is a treatment to control tumour growth and reduce symptoms in patients, especially elderly individuals and those symptomatic patients with partially resected, recurrent, or unresectable tumours [26] [27] [28] [29]. Tumour recurrence and complications following radiotherapy is observed in these subset of patients [30] [31] [32]. Traditional external beam radiotherapy therapy is rarely curative and offers little tumour control for large and extensive glomus jugulare tumours, but radiation therapy followed by surgery was found to be more successful in tumour eradication [25]. The two major histologic components of Glomus tumour are the proliferating neoplastic cell (chief cell) and the peripheral stroma. There is a dynamic interaction between the two. Each cell type responds to radiation therapy in a different manner. Following external beam radiotherapy, the local tumour control falls in the range from 61% to 94% with the radiation dose between 45 and 55 Gy [33] [34] [35] [36] [37] in 20 to 25 fractions. Clinical symptoms will be improved in 71% to 89% of patients [34] [35] [38] Improvement of hearing and disappearance of tinnitus is also reported by patients [39] [40]. 4% to 20% of patients who underwent conventional external beam radiotherapy will suffer from acute complications. They are mastoiditis, dermatitis, alopecia, mucositis, external otitis, serous otitis media, altered taste, xerostomia, cerebrovascular accident, and delayed radiation-induced neoplasms [21]. Serious and chronic radiotherapy complications are brain abscess and necrosis, osteoradionecrosis of the temporal bone and second malignant neoplasm. These complications are usually caused by excessive radiation doses. Recurrent tumour growth is often encountered [41] [42].

Newer radiotherapy techniques like Intensity modulated radiation therapy

(IMRT), Stereotactic radiosurgery (SRS), Cyberknife and Proton therapy have been evolving as adjuvant to surgery or even replacing the microsurgery in Glomus jugulare tumour [18]. While stereotactic radiosurgery alone is appropriate for some smaller tumours, larger tumours require an initial debulking surgery followed by stereotactic radiosurgery. It is also found that stereotactic radiosurgery provides symptom relief and tumour control rates that are equivalent or even superior to either surgery or traditional radiotherapy with minimal adverse effects [43] [44] [45] [46]. For extensive tumours, role of pre-operative radiotherapy has to be explored. The role of chemotherapy and peptide receptor radionuclide therapy is uncertain in Glomus jugulare tumours [1]. Mean annual growth of the tumour was estimated between 2 mm - 5 mm per year in one study [47] and 1 mm in another [48]. The tumour doubling time is widely variable, between 0.6 and 21.5 years, but overall, 60 % of tumours increase their size by $1/5^{th}$ over a period of 1 - 8 years [48]. This protracted natural history of the disease and thus necessitating the longer follow up duration poses a hurdle in adopting a proper treatment strategy. If complete cure is the aim, surgery is the choice. External beam radiotherapy is the choice if local control is the target, and to avoid post- operative morbidity. Optimal management of head and neck paraganglioma is still a debated issue. Surgery, radiotherapy or simple observation are suggested [1]. Though surgery is the most effective treatment modality, it is associated with a high morbidity rate. External beam radiotherapy approaches can prevent tumour progression, but long-term consequences are possible. A conservative approach is most desirable—to intervene if there is evidence of tumour progression or where there is concern regarding malignancy [1]. Surgery may be employed to smaller tumours in younger patients, and radiotherapy may be employed for extensive tumours in older patients. A multidisciplinary team is always needed from diagnosis to treatment and follow-up. Roles of pre and post op radiotherapy and chemotherapy are yet to be established in head and neck Paragangliomas. Newer radiotherapy techniques offer a promising outcome in the management, but long-term follow up studies are required to confirm it.

5. Conclusion

Majority of the cases (75%) were in 5^{th} or 6^{th} decade of life. Main presenting symptoms were headache and defective hearing. Major radiotherapy side effects include hearing defect, otitis and oral mucositis. 50% had intra cranially extended giant Glomus tumour in Fisch stage D. Fractionated external beam radiotherapy to a dose of 54 Gy in 30 fractions at a daily dose of 180 cGy resulted in a mean reduction of 6 mm tumour size in its greatest dimension (range 0 - 12 mm) at three months post therapy. The annual growth rate of these tumours is estimated as 1 mm [48]. 7 mm reduction of tumour size at the end of third year post therapy, from the estimated annual growth if the tumour is left untreated, proves the efficacy of fractionated radiotherapy in containing the tumour. Our results prove that fractionated external beam radiotherapy is an effective meas-

ure for local tumour control in inoperable Glomus jugulare tumour, in resource limited countries where newer radical radiotherapy techniques are not available. Small patient population, lack of volumetric quantification of tumour size are drawbacks of the study.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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