10.5005/jp-journals-10003-1051

REVIEW ARTICLE

The Role of Radiotherapy in the Management of Paraganglioma

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ABSTRACT

Paragangliomas or glomus tumors are usually low-grade hypervascular tumors occurring in various sites of the autonomic nervous system including the carotid body, glomus vagale and glomus tympanicum. Although the grading of the tumor suggests a benign clinical course, the tumor can be locally malignant and surgical management is sometimes difficult because of postoperative functional loss and local recurrence. In addition, the operative field is generally very bloody and tissue planes are not always well-defined.

Though the optimal management of paraganglioma occurs in a multidisciplinary setting, considering the excellent local control rates with primary irradiation alone, a nonsurgical definitive approach should initially be considered.

Keywords: Glomus tumors, Paraganglioma, Radiation, Chemodectoma.

OVERVIEW

Paragangliomas are usually hypervascular low-grade malignancies of neural crest origin (chief cells) arising within the autonomic nervous system. The largest clusters of these cells occur in the adrenal medulla, although other sites of involvement include the jugular foramen, the middle ear, the vagus nerves and the carotid bifurcation. Much less common presenting sites are the ciliary ganglion, nasal cavity, larynx, trachea, para-aortic region and fallopian canal. Paragangliomas are believed to store and secrete catecholamines in response to neuronal or chemical stimuli.[1]

Glomus tumors are the most common tumor of the middle ear and the second most common tumor of the temporal bone. Rare case reports have been published describing metastatic spread including lung[2] and spine.[3]

NATURAL HISTORY

The glomus jugulare was first described in 1840 by Valentin[4] as the ganglia tympanica. However, it was not until 1945, that Rosenwasser[5] described the first tumor involving this structure. These tumors (also referred to as chemodectomas) occur with an estimated annual incidence of one case per 1.3 million people.[3] These tumors (sometimes referred to as chemodectomas) occur predominantly in women, with a female to male ratio of 4:1 in the fifth and sixth decades of life.[1] They are more common on the left side, and are multicentric in 3 to 10% of sporadic cases,[6,7] increasing to 25 to 50% of patients with a familial history. The genetically linked patients express an autosomal dominant inheritance and incomplete penetrance. These specific tumors usually do not express chromaffin and are dependent on age (rare in children) and gender of the affected parent, as only children of males possessing the gene (localized to band 11q23) develop tumors.[8,9]

Because of the insidious onset of symptoms, these tumors often go unnoticed, delaying diagnosis resulting in a locally advanced presentation which further mitigates against extensive surgical resection.

Up to 4% of the tumors are functional and produce clinically significant levels of catecholamines, such as norepinephrine or dopamine with symptoms mimicking a pheochromocytoma.[6,10-12] Pheochromocytoma, parathyroid adenoma and thyroid carcinoma have been reported in association with glomus jugulare paraganglioma.[13-15] The differential diagnosis of these tumors as they occur in the neck includes carotid artery aneurysm, branchial cleft cyst, benign tumors and malignancy.[16] The differential diagnosis of tumors occurring in the temporal bone includes auditory canal polyp, acoustic neurinoma, malignancy (either primary or metastatic), cholesteatoma, histiocytosis, chronic serous otitis media and mastoiditis.

Metastases from glomus tumors occur in approximately 1 to 3% of cases[17] and are distinguished from a multicentric lesions based on location. Metastases have been found in the lung, lymph nodes, liver, vertebrae, ribs and spleen.

CLINICAL COURSE

The clinical course of glomus tumors often reflects their insidious nature of symptoms. Often, a significant delay in diagnosis occurs, and tumors may be quite large when first identified.

The most common symptoms are conductive hearing loss and pulsatile tinnitus. Other aural signs are otorrhea, hemorrhage, vertigo and the presence of a middle ear mass. Significant otalgia is uncommon. Cranial nerve (CN) involvement may produce hoarseness and dysphagia. The presence of jugular foramen syndrome (paresis of CN IX-XI) is pathognomonic for this tumor, but it usually follows one year after the initial symptoms of hearing loss and pulsatile tinnitus. Less commonly, glomus tumors produce CN VI and XI palsy or Horner syndrome.

Headache, hydrocephalus and elevated intracranial pressure may be produced by intracranial extension of the tumor. Ataxia and brainstem symptoms may also develop.

In about 2 to 4% of cases, the initial symptomatology is hypertension and tachycardia produced by catecholamines, norepinephrine or dopamine secreted by the tumor. Somatostatin, vasoactive intestinal polypeptide (VIP), and calcitonin may also be produced by these tumors. Other related symptoms include headache, perspiration, pallor and nausea.

Otoscopic examination may reveal a pulsatile, reddish-blue tumor medial to the tympanic membrane, and the audiologic exam may reveal a sensorineural hearing loss. Computed tomography (CT) scanning is superior for demonstrating the extent of bone destruction while magnetic resonance imaging (MRI) with gadolinium diethylene-triamine pentaacetic acid (DTPA) contrast is superior for delineating the soft tissue tumor limits. A combination of CT scanning and contrast enhanced MRI is the imaging regimen of choice to establish tumor extent.

Treatment of Paraganglioma

The treatment of paraganglioma has historically been controversial. It was not until the 1960s that diagnostic imaging devices (i.e. arteriography and tomography) became sophisticated enough to accommodate surgical anatomic needs. Following the technological imaging enhancements, multiple authors reported on various innovative surgical techniques.[18-23] Coincident with the development of improved surgical techniques, two staging systems were developed[20,24] (Tables 1 and 2). The Glasscock-Jackson and Fisch classifications of glomus tumors are both accepted classifications. However, the Fisch classification of glomus tumors more closely relates to mortality and morbidity.

Proponents of surgery argue from an historic standpoint and cite local control rates of 60 to 72%[25,26] or higher depending on location, although surgeries may be difficult due to the characteristic involvement of intracranial structures and bloody due to the structural nature of the tumor. Complications of surgery can be significant and debilitating. One earlier study reported serious surgical complications in 11/21 patients, including cerebrospinal fluid leaks, cranial nerve injuries and postoperative dysphagia.[27] Improved techniques have brought surgical complication and local failure rates down to the single digit range[28,29] but modern radiotherapy techniques and dosages result in essentially no serious complications.[30] However, surgery remains a viable option for properly selected patients.

Multifraction Traditional Radiotherapy

More recently, radiation therapy has demonstrated local control rates equal to, or surpassing that of surgery.[31-35] Multiple institutions have reported excellent local control of 82 to 100%[32,34,36,37] with minimal morbidity with moderate doses of 30 to 50 Gy. More recently doses of 4500 to 5040 cGy have become standardized.[16] Many of these same authors cite radiation as the treatment of choice for lesions with extensive bony involvement. Larner et al performed an extensive review covering 50 years of treatment and 36 patients.[38] At a mean follow-up of 10 years, only a single patient treated with a radiotherapy dose of less than 4000 cGy recurred, despite the fact that most of the patients treated with radiotherapy alone (11/21) were classified as McCabe-Fletcher group III (Table 3), which is least amenable to local therapy and cure. While some of the diagnostic procedures outlined in this classification are no longer performed in most institutions, the degree of local involvement clearly demonstrates the added difficulty of tumor accessibility and local control. More recently, Hinerman et al reviewed 80 cases of paraganglioma involving 71 patients treated with radiotherapy alone (72 tumors) or sub-total resection surgery followed by radiotherapy (8 tumors).[44] Radiation doses ranged from 37.7

Table 1: Glasscock-Jackson classification of glomus jugulare tumors

I.	Small tumor involving jugular bulb, middle ear and mastoid
II.	Tumor extending under internal auditory canal; may have intracranial extension
III.	Tumor extending into petrous apex; may have intracranial extension
IV.	Tumor extending beyond petrous apex into clivus or infratemporal fossa; may have intracranial extension

Table 2: Fisch classification of glomus tumors of the temporal region (revised)

A.	Tumors limited to middle ear space
B.	Tumors limited to middle ear or mastoid without involvement of the infralabyrinthine space of the temporal bone
C.	Tumors involving infralabyrinthine and apical spaces of temporal bone with extension into the apex
D1.	Tumors with intracranial extension < 2 cm in diameter
D2.	Tumors with intracranial extension > 2 cm in diameter

Table 3: McCabe and Fletcher classification

Group I (tympanic tumors)
- Absence of bone destruction on radiographic examination
- Intact cranial nerve VIII
- Intact jugular foramen
- Absence of facial weakness.

Group II (tympanomastoid tumors)
- Bone destruction confined to the mastoid
- Facial nerve normal or paretic
- Jugular foraminal nerves intact
- Superior bulb of the jugular vein involved by retrograde jugulography.

Group III (petrosal and extrapetrosal tumors)
- Destruction of the petrous bone, jugualr fossa or occipital bone on radiographic examination
- Positive retrograde jugulography
- Jugular foraminal syndrome
- Presence of metastases
- Carotid arteriogram evidence of petrous or occipital bone destruction.

to 60 Gy (mean 45.61 Gy) delivered at 1.5 to 2.0 Gy/fraction. The local control rate was 94% in all patients treated *de novo* and 96% when combining the crude rate with the radiotherapeutic salvage rate (2/4 tumors) despite the fact that 30 patients were of McCabe-Fletcher group III. No radiotherapy-alone patient developed a serious long-term complication; although a single patient developed severe mucositis requiring intravenous hydration. Powell et al observed severe complications in two of 46 patients treated with radiotherapy alone.[39] However, both of these patients received doses in excess of 60 Gy (64 and 66 Gy) which is no longer considered acceptable or necessary. There is no report of severe long-term complication in the modern literature with dose limits of 45 to 50 Gy delivered by megavoltage radiotherapy equipment.

Combination Surgery and Radiotherapy

There are no reported advantages to preplanned combination surgery and radiation therapy. Full dose radiation therapy following subtotal resection has demonstrated local control rates similar to radiation and surgery alone.[10,12,16,26,31,32,35,39,40]

Stereotactic Radiosurgery

Newer studies have advocated for stereotactic radiosurgery (SRS) in appropriately selected patients. Gottfried et al reviewed eight series of patients comprising a total of 142 cases treated with SRS (dose range 12-18 Gy) and compared these data to seven surgical series including a total of 374 patients.[40] While this meta-analysis lacks the statistical power of a prospective randomized trial (there have been no large, multi-institutional, prospective studies to date), it represents the largest total cohort of patients examined in the recent literature. Patients treated with radiotherapy tended to be older (mean 47.3 *vs* 56.7 years) and had slightly shorter follow-up (49.2 *vs* 39.4 months respectively). The local control rate of surgically treated patients was 92.1% *vs* 97.1% in radiotherapeutically treated patients, despite the fact that 52% of the radiotherapy cohort had failed prior therapy (60% had failed prior surgical therapy) and the stereotactic treatment was salvage therapy. However, the presence of residual imaging abnormality persisted in all patients treated with radiation. Twelve patients in the SRS group developed complications. In nine patients, transient cranial neuropathies developed, which resolved with expectant observation or steroid therapy. Three patients (2.1%) developed permanent facial nerve injury. There were no fatalities associated with radiosurgery. Conversely, surgical mortality was 1.3 and 8.3% of patients developed cerebrospinal fluid leaks.[40] In a study by Pollock, similar local control rates were observed using SRS with a gamma knife apparatus.[41] In a cohort of 42 patients, all but one had controlled disease. Pollock also reported similar persistent findings on follow-up imaging studies with a median follow-up of 44 months. No new cranial nerve complications developed in his series. Others have reported similar local control and complication rates;[37,38] although one of these groups (Lim et al) reported on SRS doses of up to 27 Gy.[42]

Treatment of Recurrent Disease with Radiotherapy

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.[43] 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.

CONCLUSION

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 45 Gy and dose should never exceed 50 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. Multidisciplinary management that includes the discussion of a radiotherapeutic alternative to optimize outcomes and minimize morbidity should be included prospectively in treatment management decisions. Additional data collection and study of these tumor types are necessary to further elucidate the variable natural histories of these tumors and to define radiation dose-volume response characteristics.

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