Is Regional Lymph Node Metastasis of Head and Neck Paraganglioma a Sign of Aggressive Clinical Behavior: A Clinical/Pathologic Review

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Abstract

Background: Head and neck paraganglioma is a rare neoplasm of the paraganglia. It accounts for <1% of all head and neck tumors. It usually has benign clinical course; however, malignant paraganglioma can only be diagnosed by showing metastatic disease. We undertook a retrospective study to assess the clinical significance of regional lymph nodes metastases in head and neck paragangliomas. Design: From 1993 to 2016, primary head and neck paragangliomas are identified. The patient clinical and histopathologic materials were reviewed. Results: Sixty-five specimens from 62 patients (3 patients with more than 1 specimens) with head and neck paragangliomas were recorded (49 female and 13 males) with mean age of 54 (24-78 years). The locations of the tumors were as follows: carotid body: 30, glomus tympanicum: 11, glomus jugulare: 14, parapharyngeal space: 3, and 1 case each of larynx, skull base, paraglottic area, infratemporal fossa, mastoid, cerebellopontine (CP) angle, and pyriform sinus. On histopathology, we found 5 cases of sclerosing variant. Thirty-two (52%) of the 62 patients had regional lymph node biopsy. Four (12%) of the 32 show metastatic paraganglioma (3 females and 1 male with mean age = 35). Two of the 5 cases of sclerosing variant had positive lymph nodes. No evidence of local recurrence or distant metastasis in the patients with positive lymph nodes with a 6 to 11 years follow-up. One of the 28 patients with negative lymph nodes developed metastatic disease to lumbar spine in 5 years. Conclusion: Metastatic paraganglioma to regional lymph nodes may have indolent clinical behavior, with disease-free survival of up to 11 years. The incidence of metastatic disease in lymph nodes was 4 (12%) of 32. Forty percent (2/5) of the cases with sclerosing variant of paraganglioma had lymph node metastases indicating that this tumor may have a more aggressive histological behavior.

Keywords
paraganglioma, sclerosing, head and neck, regional lymph nodes

Introduction

Paragangliomas are rare neuroendocrine tumors arising from neural crest progenitors located outside the adrenal gland. These tumors are homologous to adrenal pheochromocytomas and drive from sympathetic ganglia in abdomen and thorax (sympathetic paragangliomas) or from parasympathetic tissues in the head and neck (parasympathetic paragangliomas) regions. The clinical presentation is so variable that paraganglioma has been described as “the great masquerader.”

Head and neck paragangliomas are not common, accounting for only 0.03% of all head and neck neoplasms. Forty percent of head and neck paragangliomas occur in the jugular and vagal regions. Paragangliomas in the head and neck are typically non-secretory, in contrast to thoracic and abdominal paragangliomas,

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which are associated with the sympathetic nervous system and are typically secretory.\(^3\)

Although they are mostly benign, painless, slow-growing tumors, 10% to 20% show malignant behavior.\(^2\) To date, there are no histopathological criteria for the diagnosis of malignant paraganglioma, and the sole reliable manifestation of malignancy is the presence of distant metastasis.\(^2\)

Histologically, paraganglioma is composed of nests of tumor cells that are surrounded by highly vascular septa. The nests are composed of 2 cell types: chief cells (paraganglia cells) and sustentacular cells that form the characteristic alveolar (Zellballen) pattern. The chief cells have eosinophilic, finely granular cytoplasm and centrally located nuclei. Isolated cellular pleomorphism may be present but is prognostically not significant. Sustentacular cells are inconspicuous spindle-shaped cells surrounding the chief cells and can be best identified by S100 protein or glial fibrillary acidic protein (GFAP) immunohistochemistry. The mitotic rate is usually very low with a Ki-67 proliferation index of <3%.\(^4\)

Sclerosing paraganglioma is an unusual morphologic variant that is remarkable for the presence of prominent stromal sclerosis and hyalinization, resulting in a pseudo-infiltrative histologic growth pattern. The most important differential diagnosis is with a solitary fibrous tumor arising in the soft tissue of the head and neck.\(^5\)

Hereditary paraganglioma has been associated with multiple endocrine neoplasia type 2, von Hippel-Lindau disease, neurofibromatosis type 1, and hereditary pheochromocytoma and paraganglioma syndrome. These syndromes are caused by mutations in the RET, VHL, NF1, and SDH (SDHD, SDHB, and SDHC) genes, respectively.\(^1\)

Paragangliomas are also part of Carney triad and Carney-Stratakis syndrome although these paragangliomas show epigenetic changes involving the SDHD gene.\(^7\) The histopathologic criteria for predicting the biologic behavior of paragangliomas remain controversial. Although the presence of central necrosis, vascular or perineural invasion, and mitoses suggest malignant behavior, evidence of metastasis is currently considered to be the only reliable criterion to diagnose malignancy.\(^5\)

In 2014, Mediouni et al published a comparative retrospective study on 142 head and neck paragangliomas and found 11 (7.7%) cases of malignant paraganglioma with proven metastatic lesions involving bone, cervical lymph nodes, liver, lung, and thyroid. They concluded that malignancy was not necessarily associated with a poor short-term prognosis due to the slow course of the disease.\(^8\)

### Methods

We performed a retrospective study on primary head and neck paragangliomas from 1993 to 2016 in a single institution, and we found 62 patients with primary head and neck paragangliomas. The patient’s clinical and histopathologic data including the patient’s age, sex, tumor location, treatment, pathology of the tumor, presence or absence of metastatic disease, and patient’s long-term follow-up were reviewed. Statistical analysis was performed by unpaired \(t\) test (continuous data). The difference was considered significant when \(P\) value was <.05.

### Results

Of the 62 patients with primary head and neck paragangliomas, 49 were female and 13 were male with female–male ratio of 3.8:1. The mean age was 54 years and the age ranges from 24 to 78 years. We reviewed 64 specimens since 2 patients have more than 1 specimen (1 case of resection of recurrent disease, 1 case of multifocal disease).

The locations of the tumors were as follows: carotid body: 30, glomus tympanicum: 11, glomus jugulare: 14, parapharyngeal space: 3, and 1 case each of larynx, skull base, paraglottic area, infratemporal fossa, mastoid, cerebellopontine (CP) angle, and pyriform sinus. Thirty-two (52%) of the total 62 patients had concurrent regional lymph node biopsies at the time of surgical resection, and it ranges from 1 to 29 regional lymph nodes. The histologic examination of the 64 paraganglioma specimens show 59 cases of classic and 5 cases of sclerosing variant paragangliomas (Figure 1). Interestingly, 4 (12%) of those 32 patients with lymph node dissection showed metastatic paraganglioma involving the lymph nodes (Figures 2–5). The calculated 95% confidence interval (CI) was 4% to 28%. The cases were 3 females and 1 male patient with the mean age of 35 years.

Two of the 4 metastatic paragangliomas to the lymph nodes were sclerosing variants. The primary locations of the metastatic paragangliomas were 2 carotid body tumors, 1 in the infratemporal fossa, and 1 in glomus tympanicum.

Two of the 4 patients with metastatic disease to lymph nodes received post operation radiation therapy and shows no evidence of recurrent disease in 9- and 6-year follow-up, respectively.

Long-term follow-up of the remainder 28 patients with negative regional lymph nodes show that 1 patient with primary carotid body paraganglioma developed lumbar spine metastasis 5 years later.

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**Figure 1.** Sclerosing variant of paraganglioma.
In the total of 62 patients, 9 (14.5%) patients showed local recurrence. The calculated 95% CI was 7% to 25%. One case has documented positive margins in prior resection of the tumor. This patient had 3 negative lymph nodes (recurrence in 9 years).

Five ceases with local recurrence have regional lymph node biopsies and all 5 cases have negative lymph nodes at the time of the surgery. Among the 30 patients without regional lymph node biopsy, 4 (13%) patients showed local recurrence, one of which was already a resection of a recurrent disease. The calculated 95% CI was 4% to 30%.

Seven patients were recorded to have positive margins/partial resection of the tumor. Two of them (2/7) received postoperative radiation with residual stable disease in 1- and 9-year follow-ups, respectively. One case showed recurrence in 9 years (see above) and received radiation after resection of the recurrent disease. Other cases have incomplete follow-up data.

Based on our medical records, we were able to find only 5 cases of post operative radiation therapy. The reasons for the radiation therapy include positive lymph nodes in 2 cases, incomplete excisions in 2 cases, and local recurrence in 1 case.

Multifocal lesions were present in 2 patients, 1 with 2 lesions in pyriform sinus and para glottic sinus (both resected) and 1 with bilateral carotid body tumors (only resected on 1 side). The mean age of the patients with local and distant metastasis (5 total patients) was 38.6, and the mean age of the remaining 57 patients was 56 years. The significance of the age difference between the 2 groups was calculated by unpaired t test and was statistically significant (P value = .0049). The summary of the results is presented in Table 1.
| Age | Sex | Size | Location | Lymph Node | Follow-Up (F/U) | Pertinent Histologic Findings |
|-----|-----|------|----------|------------|----------------|-----------------------------|
| 27  | F   | N/A  | Carotid body | 1 positive Lymph node | Received radiation-no recurrence in 9 years follow-up | sclerosing |
| 48  | F   | N/A  | Infratemporal fossa | 1/17 positive Lymph node | Postoperative radiation, no recurrence in 6 years | |
| 34  | F   | 3 cm | Carotid body | 1/2 positive | N/A | sclerosing |
| 33  | M   | N/A  | Glomus tympanicum | 1/4 positive Lymph node | N/A | |
| 36  | F   | 6 cm | Carotid body | 1 negative lymph node | N/A | |
| 47  | F   | 4 cm | Carotid body | 1 negative lymph node | No recurrence in 11 years | N/A |
| 54  | M   | 3.9 cm | Carotid body | 1 negative lymph node | N/A, positive margin | |
| 58  | F   | N/A  | carotid body | 1 negative lymph node | N/A | |
| 53  | F   | 3.4 cm | Parapharyngeal space | 11 negative lymph nodes | N/A after 4 months | |
| 34  | F   | 0.9 cm | Glomus jugulare | 11 negative lymph nodes | Partially excised, N/A | |
| 43  | F   | Fragments | Glomus jugulare | 17 negative lymph nodes | Radiologic recurrence in 7 years | |
| 49  | M   | Fragments | Glomus jugulare | 17 negative lymph nodes | Positive margin, radiation, residual disease in 1-year F/U | |
| 72  | F   | 2.5 cm | Carotid body | 2 negative lymph nodes | No recurrence in 8 years | |
| 54  | F   | 3.8 cm | Carotid body | 2 negative lymph nodes | No recurrence in 3 years | |
| 46  | F   | Fragments | Glomus tympanicum | 2 negative lymph nodes | N/A | |
| 41  | F   | 4.5 cm | carotid body | 2 negative lymph nodes, | 5 months F/U, no recurrence | Marked pleomorphism |
| 56  | F   | 1.5 cm | carotid body | 29 negative Lymph nodes | No recurrence, 1-year F/U | |
| 70-79 | M | Fragments | Glomus jugulare | 3 negative lymph nodes in first resection | Partial resection, recurrent in 9 years, radiation after recurrence. No more lesion in 3 years | Bone invasion in recurrent |
| 78  | F   | 5 cm | Carotid body | 3 negative Lymph nodes | N/A | |
| 70  | F   | 2.5 cm | Carotid body | 3 negative lymph nodes | No recurrence in 9 years | |
| 51  | F   | 1.4 cm | Carotid body | 3 negative lymph nodes | N/A | |
| 61  | F   | 4.8 cm | Skull base | 3 negative lymph nodes | N/A | |
| 69  | F   | 5 cm | Carotid body | 3 negative lymph nodes on 1st resection | Bilateral tumor, R: 2005, L: 2008 resected elsewhere, no recurrence after 2nd surgery | |
| 39  | F   | 3 cm | Carotid body | 5 negative lymph nodes | N/A | Vascular invasion |
| 54  | F   | 1.6 and 3.8 cm | Multiple carotid body and parapharyngeal space | 5 negative lymph nodes | No recurrence in 2 years F/U | |
| 42  | F   | Fragments | Glomus tympanicum | 5 negative lymph nodes | N/A | |
| 52  | F   | 4.9 cm | Glomus jugulare | 5 negative lymph nodes | Radiologic recurrence in 1 year | |
| 51  | M   | 5.5 cm | carotid body | 5 negative Lymph nodes | Mets on 2015 in L spine | |
| 39  | F   | 2.5 cm | Carotid body | 8 negative Lymph nodes | N/A | |
| 41  | F   | 3 cm | Glomus tympanicum | 9 negative Lymph nodes | Radiologic recurrence in 2 years | |
| 44  | F   | 1.5 cm | Carotid body | Lymph node negative | No recurrence in 2 years | |
| 59  | F   | 3 cm | Glomus jugulare | 6 years F/U, no recurrence | |
| 73  | F   | 5 cm | Carotid body | No recurrence in 2 years | |
| 48  | F   | Fragments | Mastoid and glomus tympanicum | 8 negative Lymph nodes | Already a recurrent tumor N/A | |
| 59  | F   | Carotid body | N/A | Vascular invasion | |
| 45  | F   | 2.5 cm | Carotid body | N/A | |
| 68  | F   | 4.5 cm | Carotid body | No recurrence in 13 years | sclerosing, vascular invasion |
| 66  | F   | 3.5 cm | Larynx | N/A | |
| 50  | F   | 1.9 cm | Carotid body | N/A | |
| 49  | F   | 1.5 cm | Glomus jugulare | No recurrence in 1 year | |
| 58  | F   | 0.4 cm | Glomus jugulare | N/A | |
| 81  | F   | N/A | CP angle | N/A | |
| 53  | F   | 7 cm | Glomus tympanicum | No recurrence in 16 years | Increased mitosis | |
| 70  | F   | Fragments | Glomus tympanicum | No recurrence in 14 years | |
Discussion and Conclusion

Head and neck paragangliomas are uncommon tumors and are usually managed by surgical resection. In concordance to prior data in the literature, our data showed that head and neck paragangliomas occur in the carotid body (31/62) and are more frequent in females with female–male ratio of 3.8:1.

One explanation for female predilection is the higher sensitivity of hypoxia in females as a result of the lower baseline hemoglobin in comparison to males. Hypoxia induces hyperplasia of the chemoreceptors. Consequently, paragangliomas are 10 times more prevalent at high altitude. Forty-eight percent (30/62) of our head and neck paragangliomas originated from carotid bodies. The calculated 95% CI is 36% to 60%.

In the neck, other important differential diagnosis of carotid body paragangliomas are neuroendocrine tumors, medullary thyroid carcinomas, hyalinizing trabecular tumors of the thyroid, and parathyroid adenomas. Negative epithelial markers by immunohistochemical stains, including pan cytokeratin, can differentiate most paragangliomas from morphologically similar thyroid carcinomas, parathyroid lesions, and neuroendocrine tumors.

We documented pertinent positive histologic findings including vascular invasion (4 cases), increased mitosis (2 cases), profound pleomorphism/anaplasia (2 cases), anaplasia (1 case), and invasion to adjacent bone (1 case). Vascular invasion was the most frequent pertinent positive finding. In the 4 cases with vascular invasion, none showed recurrent or metastatic disease (Figure 6).

The definition of increased mitosis is not well described in the literature, and we considered increased mitosis in our cases if there were more than 2 per 50 high-power fields or if there was an abnormal mitotic figure. We found 2 cases of increased mitosis one of which has concurrent bone invasion. The case with concurrent bone invasion showed evidence of recurrence in surveillance CT scans after 11 years.

There were 2 cases of adjacent bone invasion. One case (see above) with concurrent increased mitosis showed recurrent disease, and the other lesion was a recurrent lesion in a patient.

### Table 1. (continued)

| Age | Sex | Size | Location | Lymph Node | Follow-Up (F/U) | Pertinent Histologic Findings |
|-----|-----|------|----------|------------|----------------|-------------------------------|
| 61  | F   | Fragments | Glomus tympanicum | No recurrence in 5 years |                |                               |
| 69  | F   | Fragments | Glomus tympanicum | Radiologic recurrent in 11 years |                |                               |
| 48  | F   | Fragments | Glomus tympanicum | Partial excision, stable disease in 9 years |                |                               |
| 64  | F   | N/A  | Glomus jugulare | No recurrence in 6 years |                |                               |
| 45  | F   | Fragments | Glomus jugulare | N/A, partially excised |                |                               |
| 48  | F   | Fragments | Glomus jugulare | No recurrence in 1-year F/U |                |                               |
| 77  | F   | Fragments | Glomus jugulare | Residual stable disease, partially excised in 5-years F/U |                |                               |
| 65  | F   | Fragments | Glomus tympanicum | No recurrence, 1-year F/U |                |                               |
| 68  | F   | N/A  | Glomus jugulare | Radiologic recurrence on 17 years |                |                               |
| 58  | M   | 7 cm | Carotid body | N/A |                | Sclerosing, marked pleomorphism |
| 49  | M   | 7 cm | Carotid body | N/A |                |                               |
| 29  | M   | 3.5 cm | Carotid body | N/A |                |                               |
| 31  | M   | 3.5 cm | Carotid body | N/A |                |                               |
| 70  | M   | 8.5 cm | Parapharyngeal space | No recurrence in 1-year F/U |                |                               |
| 72  | M   | 1.2 cm | Glomus jugulare | N/A |                |                               |
| 77  | M   | Fragments and 3.8 cm | Pyriform sinus para glottic mass | Multifocal disease, No recurrence in 6 months |                |                               |
| 59  | M   | N/A  | Glomus jugulare | Radiologic recurrence in 11 years |                | Bone invasion, increased mitosis |

Abbreviations: CP, Cerebellopontine angle; F, female; F/U, follow-up; M, male; NA, Not applicable.
with prior paraganglioma of glomus jugulare and partial resection. This patient was treated with surgical resection and postoperative radiation therapy.

Some degrees of nuclear pleomorphism is usually accepted in paragangliomas, but profound nuclear pleomorphism is considered worrisome by some experts. We found 2 cases of marked nuclear pleomorphism in our series (Figure 7). One patient was a young man (29 years old) with sclerosing variant paraganglioma of the carotid body. We suspected that based on the location of the tumor, his young age, and worrisome histologic features including sclerosing variant paraganglioma and nuclear pleomorphism, he is a high-risk patient for local recurrence and/or metastatic lesions. Unfortunately, this patient lost the follow-up.

Interestingly, 2 cases of sclerosing variant paragangliomas showed concurrent marked pleomorphism and vascular invasion as well. Follow-up was available in 1 of them, and this patient showed no local recurrence or regional and distal metastasis. We did not encounter any case with central necrosis among our patients. In summary, among our 9 cases with more worrisome histological features (vascular invasion, bone invasion, increased mitosis, marked pleomorphism), none showed regional or distant metastasis and both cases of bone invasion (with or without increase mitosis) were associated with local disease recurrence.

On the other hand, among 5 cases of sclerosing variant paragangliomas, 2 (40%) of 5 cases were associated with positive regional lymph nodes. However, due to small number of patients, the calculated 95% CI is 11% to 77%.

In our study, we found 12% of the examined cases with regional lymph nodes metastasis (4/32). Nine- and 6-year follow-ups were available in 2 of the 4 cases and showed no evidence of distant metastasis.

We found one (1/62) case with distant metastasis to lumbar spine. This patient had 5.5 cm carotid body paraganglioma with no worrisome histologic features and 5 negative lymph nodes at the time of surgery. He presented with metastatic disease 5 years after the original resection.

Prior studies also showed that while most metastases in head and neck paragangliomas are confined to the regional lymph nodes, distant metastases do occur, usually to the lung and bone. The likelihood of malignancy may also be affected by the location of the neoplasm and is reported to be 5% for temporal bone paragangliomas. In addition, 15% of carotid body/glomus vagal tumors are generally found to be malignant.

Several independent risk factors for metastatic paraganglioma were recognized, which included the presence of SDHB mutations, extra-adrenal location, size of the primary tumor > 5 cm (in SDHB-related paragangliomas over 3.5 cm), younger age at initial diagnosis, and elevated 3-methoxytyramine levels.

In a study by Nishijima et al in 2011 on malignant carotid body paragangliomas with distant metastasis, the authors mentioned that patients with malignant paragangliomas with distant metastasis appear to have a poor prognosis compared to patients with only regional spread of disease. Moreover, the report states that not all cases with distant metastasis necessarily have a bad prognosis.

We focused our study to primary head and neck paragangliomas, however, excluded from our study series, there were 3 patients with “secondary” head and neck paragangliomas (2 metastatic disease and 1 case of possible metastatic vs second primary in a patient with prior pheochromocytoma). SDHB germline mutation was detected in one of the above cases with extensive metastatic paragangliomas including a 5.1 cm frontal mass and multiple positive lymph nodes.

The significance of identifying paragangliomas with regional lymph node metastasis, their management, and prognostic importance is not well documented in the literature.

Radiofrequency ablation, external radiation, and radiotherapy with 131I-metaiodobenzylguanidine (MIBG) can be used in patients with metastatic disease. External beam radiation is a common treatment modality in patients with inoperable head and neck paragangliomas.

In one study, long-term results of external-beam radiotherapy, and stereotactic radiosurgery for paragangliomas were investigated in 33 cases. In the median follow-up of 13 years, no patient had developed a radiation-induced malignancy and the 10-year tumor control rate was 92%.

According to the literature, malignant paragangliomas are indolent but progressive, resulting in less than 50% overall 10-year survival. Surgical debulking of the tumors along with symptomatic therapy with β and α blockers (for secretory paragangliomas) are the treatments of choice for metastatic disease. Radiation can slow the disease progression. However, it does not improve the survival.

In summary, primary head and neck paragangliomas with regional lymph node metastasis appears to have a favorable clinical course. In our series, the patients with positive lymph nodes (2 of 4 with available follow ups) did not show distant metastasis and the only patient with distant metastasis had negative regional lymph nodes.

We documented 5 of 62 cases of metastatic paragangliomas (4 to lymph nodes and 1 to bone) in primary head and neck paragangliomas. The clinical factors associated with local and

Figure 7. Nuclear pleomorphism in paraganglioma.
distant metastasis were young age (mean: 38.6 years), female
gender (3 females and 2 males), and carotid body location
(3 cases), although the age is the only parameter that was
statistically significant (P value = .0049).

The limitations of our study include unavailability of clinical
data and follow-ups in some cases (consults, old cases) and
unavailability of immunohistochemical stains for SDHB pro-
teins. Rarity of this disease and its indolent course which
requires long-term follow-ups are challenges in the studies of
paragangliomas. Larger studies may enlighten further under-
standing of the disease pathophysiology and management.

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