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Second primary tumors in patients with a head and neck paraganglioma

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Abstract

Background: There are conflicting recommendations and possibly overuse of imaging for surveillance of second primary tumors for patients with a history of head and neck paraganglioma.

Methods: Retrospective cohort study of 234 adults with head and neck paragangliomas (1990-2010) followed for a mean of 7.5 ± 8.4 years.

Results: The rate of second paraganglioma was 1.7% after 5 years and 5.1% after 10 years, yielding an incidence of 6.65 per 1000 person-years. Only 1.3% of patients (2.59 per 1000 person-years) ever had a second paraganglioma in the chest, abdomen, or pelvis. Patients with a hereditary paraganglioma (hazard ratio [HR] = 4.84, 95% confidence interval [CI]: 1.52-15.43) or carotid body tumor (HR = 3.55, 95% CI: 1.15-10.99) were at greater risk.

Conclusions: The incidence rate of a second primary paragangliomas is low but increases with hereditary disease. These results question the utility of repeated imaging outside of the neck to screen for second paragangliomas.

KEYWORDS

glomus tumor, imaging, paraganglioma, second primary tumor, surveillance

1 | INTRODUCTION

Paragangliomas are typically hypervascular, slow-growing tumors, occurring in 1 in 30 000 to 1 in 100 000 people.[1,2] Extra-adrenal parasympathetic paragangliomas are most likely found in the head and neck.[3] However, only 3% to 18% of all paragangliomas occur within the head and neck region, the rest occurring primarily in the chest, abdomen, or pelvis.[4-7]

There is a known predilection toward multicentricity. The likelihood of having numerous paragangliomas is suspected to be 10% to 15%.[8,9] With hereditary disease, the percent of patients with numerous paragangliomas is questioned to be as high as 30% to 50%.[10-12] Prior studies have emphasized the importance of imaging in the surveillance of paragangliomas; however, there are inconsistent recommendations from medical societies regarding frequency and location.[13-15] Without evidence-based guidelines available, some clinicians conduct as frequent as annual imaging of the neck, chest, abdomen, and pelvis for patients with a history of head and neck paraganglioma to evaluate for new tumors.[16,17]

To our knowledge, no studies to date have reported the incidence of second primary tumors in patients with a history of head and neck paraganglioma. Furthermore, there is minimal data on what factors should guide clinicians in the role of repeated imaging in the surveillance of paragangliomas. Numerous studies have noted a need for more longitudinal data in order to inform validated protocols on serial imaging of patients with paraganglioma.[13,16,18]

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In this long-term, retrospective cohort study, we investigate the incidence rate of second primary paragangliomas in patients with a history of head and neck paraganglioma. We characterize what factors predict the course of disease for patients with a paraganglioma to guide clinicians on the use of serial imaging.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

We conducted a retrospective chart review of patients who had a diagnosis of paraganglioma between 1990 and 2010 based on International Classification of Diseases, Ninth Revision: malignant neoplasm of carotid body (194.5), malignant neoplasm of aortic body and other paraganglia (194.6), benign neoplasm of carotid body (227.5), benign neoplasm of aortic body and other paraganglia (227.6), and neoplasm of uncertain behavior of paraganglia (237.3). Patients who did not have a diagnosis of a head and neck paraganglioma nor substantive follow-up were excluded from the study. Our analytic cohort was ultimately comprised of individuals with at least one post-treatment image of the neck, chest, abdomen, and pelvis. Discrepancies or ambiguity in coding were reconciled by a senior reviewer. Patient follow-up began on the date of their treatment or the date of diagnosis if the paraganglioma was being clinically observed. This study was approved by the Cleveland Clinic Institutional Review Board (IRB 17-728), which waived the need for written informed consent.

2.2 | Imaging

Imaging was included if it was done for any reason, including those not specific to paraganglioma surveillance. Appropriate diagnostic imaging of the head and neck included CT, MRI, ultrasound, or angiography. Appropriate diagnostic imaging of the chest, abdomen, or pelvis included CT, MRI, and nuclear medicine imaging (eg, octreotide, positron emission tomography, metaiodobenzylguanidine, or gallium). We did not include standard radiographs or ultrasounds of the chest, abdomen, or pelvis as adequate oncologic screening tools.

2.3 | Covariates

Age was recorded based on the patient's age at the time of diagnosis. Sex was self-reported. Tumor type (ie, carotid body tumor, glomus jugulare, glomus vagale, or glomus tympanicum) was determined based on surgical pathology or diagnostic radiology. In patients who initially was seen with numerous paragangliomas of the head and neck, the larger tumor was considered primary. Patients were noted to have a hereditary paraganglioma if they were found to have mutations in succinate dehydrogenase (SDH) B, C, and D, Von Hippel Lindau, or RET oncogene.

2.4 | Statistical analysis

Demographic and clinical characteristics were compared with chi-squared or *t* tests where appropriate. Cox proportional hazards regression analysis was performed to determine the factors associated with a risk of second primary paraganglioma. Patients were followed from the date they were first diagnosed/treated with a head and neck paraganglioma until they were diagnosed with a second primary paraganglioma anywhere in the body or were censored at the date of their last imaging (head, neck, chest, abdomen, or pelvis). Significance testing was performed using two-sided tests with a type I error rate of 0.05. Statistical analyses were done using SAS v 9.4 (SAS Institute, Cary, North Carolina) and Stata 12 (StataCorp, Texas).

3 | RESULTS

Table 1 describes the demographic and clinical characteristics of the study population. The mean follow-up duration was 7.5 ± 8.4 (SD) years (median of 4.9). Our population included patients with a primary diagnosis of carotid body (42.7%), glomus jugulare (26.5%), glomus tympanicum (18.8%), and glomus vagale tumors (12.0%). Most patients underwent surgical resection (57.3%), compared to observation (21.8%), radiation (16.2%), or surgery with radiation (4.7%). Patients had a mean of 6.4 ± 7.7 (SD) surveillance images of the head and neck. Twenty-six percent (61 of 234) of patients had imaging of the chest or abdomen/pelvis explicitly to screen for second primary paragangliomas (all other patients had imaging for other reasons).

In our analytic cohort of 234 patients, 14 patients (6.0%) were found to have a second primary paraganglioma. Within the head and neck, these included three carotid body tumors, two glomus jugulares, three glomus vagales, and three unspecified neck paragangliomas. Only three patients (1.3%) were found to have second primary paraganglioma outside the head and neck, including a pheochromocytoma, abdominal aortic paraganglioma, and mediastinal paraganglioma. Twenty seven of the 34 patients (79%) who underwent genetic analysis were positive. Of the 14 patients with a second primary paraganglioma, 8 patients underwent genetic analysis. One hundred percent (8 of 8) of these patients had a hereditary paraganglioma (three SDHB and five SDHD), including all three patients with paragangliomas occurring outside of the head and neck. None of the seven patients with negative genetic analyses had a second primary paraganglioma.

Figure 1 depicts patient survival without a second primary paraganglioma after being treated for a head and neck

TABLE 1 Demographic and clinical characteristics of patients with a history of head and neck paraganglioma

Variable	Did not develop second paraganglioma (n = 220)	Developed second paraganglioma (n = 14)	Total (n = 234)	*P* value
Age at diagnosis, y, mean (SD)	54.8 (16.4)	46.8 (19.7)	54.3 (16.7)	.42
Sex, n (%)				
Woman	156 (70.9)	8 (57.1)	164 (70.1)	.37
Man	64 (29.1)	6 (42.9)	70 (29.9)	
Diagnosis, n (%)				
Carotid body tumor	91 (41.5)	9 (64.3)	100 (42.7)	.20
Glomus jugulare	58 (26.4)	4 (28.6)	62 (26.5)	
Glomus tympanicum	44 (20.0)	0 (0.0)	44 (18.8)	
Glomus vagale	27 (12.3)	1 (7.1)	28 (12.0)	
Multiple paragangliomas on presentation, n (%)	17 (7.7)	3 (21.4)	20 (8.5)	.39
Hereditary paraganglioma, n (%)				
Positive	19 (8.6)	8 (57.1)	27 (11.5)	<.001
Negative or unknown	201 (91.3)	6 (42.9)	207 (88.5)	

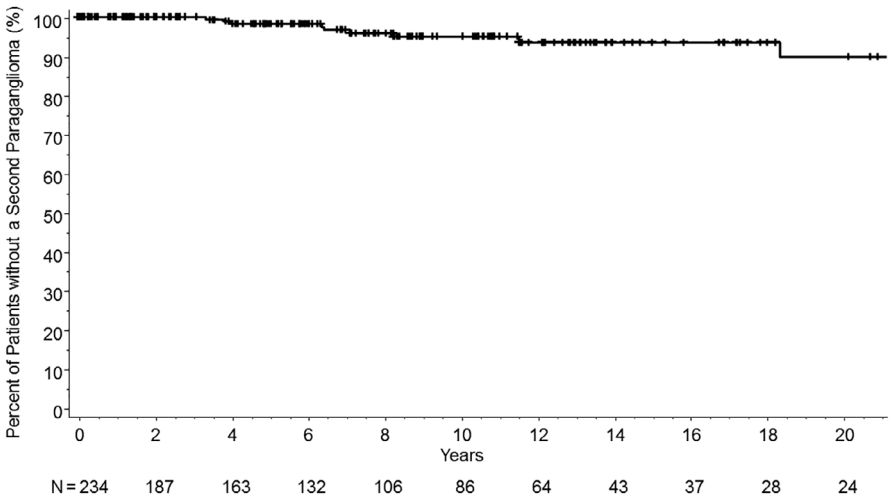

FIGURE 1 Kaplan-Meier curve for overall survival without a second primary tumor in patients with a history of head and neck paraganglioma. Tick marks represent censored observations

paraganglioma. The rate of second paragangliomas was 1.7% (95% CI: 0.0%-3.6%) after 5 years and 5.1% (95% CI: 1.3%-8.9%) after 10 years. The overall incidence of second primary paragangliomas was 6.65 per 1000 person-years. The incidence of second primary paragangliomas of the chest, abdomen, or pelvis was 2.59 per 1000 person-years.

Table 2 displays the potential factors associated with a greater risk of a second primary paraganglioma. Patients with hereditary paraganglioma were at greater risk of a second primary tumor (HR [hazard ratio] = 4.84, 95% confidence interval [CI]: 1.52-15.43) compared to patients with negative or no genetic testing. Patients with carotid body tumors were at greater risk (HR = 3.55, 95% CI: 1.15-10.99) compared to all other patients combined. There was not a statistically significant risk for patients who were younger (HR = 1.02, 95% CI: 0.98-1.06), women (HR = 0.73, 95% CI: 0.22-2.40), or had multiple paragangliomas on presentation (HR = 1.96, 95% CI: 0.42-9.09).

4 | DISCUSSION

In patients with a history of head and neck paraganglioma, second primary paragangliomas are rare, especially within the chest, abdomen, and pelvis. However, patients with a

TABLE 2 Cox proportional hazards model for second primary paraganglioma

Variable	Hazard ratio	95% confidence interval	*P* value
Age	1.016	(0.98-1.06)	.42
Sex (woman vs man)	0.734	(0.22-2.40)	.61
Hereditary paraganglioma (positive vs negative or unknown)	4.841	(1.52-15.43)	.008
Type (carotid body tumor vs other)	3.546	(1.15-10.99)	.03
Multiple paragangliomas on presentation (yes vs no)	1.961	(0.42-9.09)	.39

hereditary paraganglioma or a carotid body tumor are at greater risk. To our knowledge, this study represents the largest single head and neck paraganglioma population to date and the first study to assess the incidence rate of second primary paragangliomas. Our results do not support the utility of repeated surveillance imaging of the chest, abdomen, and pelvis to screen for new tumors for patients with a history of head and neck paraganglioma.

We recommend against the use of annual imaging of the chest, abdomen, or pelvis to screen for second primary paragangliomas in patients followed for a head and neck paraganglioma, particularly if the patient does not have hereditary disease. In our population, a quarter of patients had such imaging. Although our study did not investigate paraganglioma workup, it may be appropriate to screen a patient's chest, abdomen, and pelvis at the time of initial diagnosis, particularly if there is hereditary paraganglioma or concern for metastasis. Our recommendation appears to be in line with the Endocrine Society clinical practice guidelines, which recommend that screening imaging only be "initiated once there is clear biochemical evidence of a paraganglioma."[15] Notably, the task force reports being unable to give specific recommendations related to patients with head and neck paragangliomas, the majority of which are not biochemically active.[19]

Our study appears at odds with the European Society of Endocrinology clinical practice guidelines, which recommend repeated imaging every 1 to 2 years for at least 10 years. They noted, however, that their opinion was ultimately "arbitrary," as "there are no observational or randomized studies that support any particular interval," which was accurate prior to the release of this study.[16] Based on our reported incidence rate (2.59 second primary paragangliomas of the chest, abdomen or pelvis per 1000 person-years), 38 patients would have to get a decade of annual MRIs of the chest, abdomen, and pelvis to identify a single second paraganglioma. Given the growing demand for medical financial stewardship, the cost of such screening appears to exceed the potential benefit, especially as many paragangliomas are ultimately observed without intervention.[20] Alternatively, the use of assays of plasma or urinary catecholamines may be of greater value.[19,21] The utility of biochemical screening was not examined in this study but would benefit from further research.

There is limited research into the optimal frequency of surveillance imaging of the head and neck for patients treated for a paraganglioma. A recent clinical review by Moore, Netterville, Mendenhall, Isaacson, and Nussenbaum recommended repeat imaging every 6 to 12 months for patients with head and neck paragangliomas being observed without treatment.[18] Frequency of repeat imaging of the neck must balance both surveillance for a second paraganglioma and recurrence of the primary paraganglioma. This study did not evaluate for recurrence of the initial primary paraganglioma; thus, it is difficult to provide comprehensive, evidence-based recommendations on the frequency of interval neck imaging. Based on our results and prior literature, surveillance imaging of the neck seems appropriate every several years, with a greater frequency in patients with a hereditary paraganglioma, recent treatment, or a carotid body tumor.[22-25]

Other studies have noted that genetic analysis is a critical factor in determining frequency of imaging of the neck.[26,27] Eijkelenkamp followed 91 patients with known SDHB mutations and found that 35% of patients had paragangliomas by 60 years of age.[22] They recommended surveillance imaging for head and neck paragangliomas every 3.2 years based on a Poisson approach. Others have recommended screening every 1 to 2 years in a similar population.[28,29]

We found that patients with carotid body tumors were at greater risk of a second primary paraganglioma compared to glomus vagale, glomus typanicum, and glomus jugulare tumors combined. This propensity for multicentricity has been suggested in several small case series, but this is the first study to our knowledge to demonstrate this increased risk.[30-32] Our study is not robust enough to determine if this is truly an independent risk or confounded by a greater proportion of genetic mutations with carotid body tumors.[33,34]

We found no increased risk for patients who were younger or women. Patients who was seen with multiple paragangliomas were observed to have a higher rate of developing second primary tumors; however, this was not statistically significant. This may be explained by multicentricity serving as a surrogate marker for hereditary paraganglioma, which can help inform clinicians if patients are unable to undergo formal genetic testing.[9]

Our study has limitations. There is a potential for selection bias as patients with additional tumors are more likely to follow-up. This risk is mitigated by our inclusion of imaging done for any reason—in fact, most imaging of the chest, abdomen, and pelvis was done for reasons other than

surveillance related to paragangliomas. This bias would tend to overestimate the incidence rate of second primary paragangliomas and further support our recommendations for limited surveillance imaging. To the contrary, imaging not done for tumor surveillance may be more likely to miss small or less clinically relevant paragangliomas.

Although our population is, to our knowledge, the largest collection of patients with head and neck paragangliomas to date, our sample size limited our analysis in several ways. Carotid body tumors had the highest incidence of second primary paragangliomas and were compared to all other tumors combined, as opposed to comparing each tumor individually. Our sample was also limited in the number of patients who underwent genetic testing. As so few patients actually had negative testing, genetic analysis was treated as a binary variable, with negative and nontested patients combined. There appeared to be a significant sampling bias as the vast majority of patients who underwent genetic testing were positive. At 79%, our study likely overestimates the rate of hereditary paraganglioma compared to other studies, which found rates between 34% and 50%.[35-37] These findings highlight our recommendation for genetic testing to guide in clinical management. Future studies are needed to elucidate differences between specific mutations.

5 | CONCLUSIONS

This study seeks to guide clinicians who are following patients with a history of head and neck paraganglioma based on the largest sample of this population to date. To our knowledge, this is the first study to report the incidence rate of second primary paragangliomas.

In patients with a prior head and neck paraganglioma, the development of a second paraganglioma is rare, happening in less than 2% of patients at 5 years. The incidence of a second paraganglioma occurring in the chest, abdomen, or pelvis was 2.59 per 1000 person-years, meaning 38 patients would need to undergo repeated imaging for a decade to find a single paraganglioma. Our results do not support the utility of annual imaging of the chest, abdomen, and pelvis when following a patient with a history of a head and neck paraganglioma, particularly if there is not a hereditary disease. The determination of repeat imaging of the head and neck is multifactorial but appears appropriate every several years with more frequent imaging in patients with a hereditary paraganglioma or carotid body tumor.

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