

Clinical Features, Treatment Patterns, and Factors Associated with Survival for Head and Neck Paraganglioma

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1 – INTRODUCTION

Paraganglioma are rare neuroendocrine tumors arising from neural crest-derived cells associated with the autonomic nervous system of the head, neck, thorax, and abdomen. Incidence of these tumors is estimated to be between 0.6 to 1.0 per 100,000 person-years, with 3% to 18% occurring within the head and neck. Head and neck paraganglioma (HNP) most often arise from the carotid body, middle ear, jugular bulb, and vagus nerve. If left untreated, it may cause significant morbidity and mortality by local invasion or metastasis. HNP are considered to be benign, with metastases identified in about 10% patients. Studies exploring relationships between histopathology, malignancy, and prognosis have been limited by the low statistical power inherent to a rare tumor entity. Currently there is no validated, widely accepted risk assessment method to evaluate paraganglioma behavior. The Fisch, Glasscock-Jackson, and Shamblin classification systems are narrowly applicable to specific HNP sites and fail to incorporate risk of regional or distant metastatic spread. The aim of this study was to identify HNP phenotypes in order to stratify outcomes and guide clinical management. This represents the largest analysis to date evaluating prognostic factors in HNP and the first study to stratify HNP by local tumor behavior.

2 – METHODS

We conducted a retrospective analysis of 525 adult patients (≥18 years) with primary paraganglioma of the head and neck region from 2004 through 2016 using the United States National Cancer Database (NCDB). NCDB classifies all tumors with a behavior code based on histological, cytological, or radiological findings. This behavior code gives insight into the local behavior of a tumor rather than information regarding regional or distant metastasis. All data were analyzed with Stata/SE version 16.0 for Mac. Population characteristics were compared by tumor behavior using t-test or Pearson’s chi-square test for continuous and categorical variables respectively. Cox proportional hazards modeling was used to generate unadjusted and adjusted hazard ratios (HR and aHR, respectively) with 95% confidence interval (95%CI) evaluating overall survival stratified by tumor behavior.

Table 1. Diagnostic Confirmation for HNP Cohort

Diagnostic Method:	n (%)
Positive histology	406 (77.33)
Positive cytology	2 (0.38)
Positive microscopic confirmation, method not specified ^a	1 (0.19)
Direct visualization without microscopic confirmation ^b	1 (0.19)
Radiography and other imaging techniques without microscopic confirmation	112 (21.33)
Clinical diagnosis only (other than 5, 6, or 7) ^c	2 (0.38)
Unknown whether or not microscopically confirmed ^d	1 (0.19)

^a Unknown whether histology or cytology
^b The tumor was visualized during a surgical/endoscopic procedure only with no tissue resected for microscopic examination
^c The malignancy was reported by the physician in the medical record.
^d A statement of malignancy was reported in the medical record, but there is no statement of how the cancer was diagnosed

3 – CLINICAL CHARACTERISTICS

Benign and borderline HNP have significantly different clinical characteristics compared with locally invasive HNP.

Table 2. Clinical Characteristics Stratified by Local Tumor Behavior

	Overall	Benign	Borderline	Locally Invasive	Benign vs Locally Invasive	Borderline vs Locally Invasive	Benign vs Borderline
Clinical Characteristics:	n = 525	n = 85 (16.19)	n = 199 (37.9)	n =241 (45.9)	p-value	p-value	p-value
Age at Diagnosis, y, mean (SD)	52.59 (15.9)	56.2 (15.79)	54.93 (14.38)	49.38 (16.56)	0.0005	0.0001	0.255
Primary Site, ^a n (%)					<0.0001	<0.0001	0.012
Carotid body	177 (33.71)	0 (0)	0 (0)	177 (73.44)			
Intracranial	152 (28.95)	53 (62.35)	90 (45.23)	9 (3.73)			
Cranial nerves ^b	134 (25.52)	24 (28.24)	98 (49.25)	12 (4.98)			
Skin, connective tissue, lymphatics	17 (3.24)	0 (0)	0 (0)	17 (7.05)			
Pituitary, pineal, other endocrine structures	15 (2.86)	5 (5.88)	7 (3.52)	3 (1.24)			
Acoustic nerve	7 (1.33)	3 (3.53)	4 (2.01)	0 (0)			
Peripheral and autonomic nerves	6 (1.14)	0 (0)	0 (0)	6 (2.49)			
Middle ear	4 (0.76)	0 (0)	0 (0)	4 (1.66)			
Salivary gland	4 (0.76)	0 (0)	0 (0)	4 (1.66)			
Nasal cavity/Nasopharynx/Sinus	4 (0.76)	0 (0)	0 (0)	4 (1.66)			
Oral cavity	3 (0.57)	0 (0)	0 (0)	3 (1.24)			
Oropharynx	2 (0.38)	0 (0)	0 (0)	2 (0.83)			
Median tumor size, cm (IQR)	3.5 (2.5)	3 (2)	3 (2.4)	4 (2.6)			
Regional lymph node status, n (%)							
Negative	25 (4.76)	0 (0)	0 (0)	25 (10.37)			
Positive	104 (19.81)	0 (0)	0 (0)	104 (43.15)			
No Lymphadenectomy	396 (75.43)	85 (100)	199 (100)	112 (46.47)			
Distant metastasis status, n (%)					<0.0001	<0.0001	0.492
Negative	407 (77.52)	78 (91.76)	165 (82.91)	164 (68.05)			
Positive	37 (7.05)	0 (0)	1 (0.5)	36 (14.94)			
Missing/unknown	81 (15.43)	7 (8.24)	33 (16.58)	41 (17.01)			
Overall treatment, n (%)					<0.0001	<0.0001	0.206
Surgery only	251 (47.81)	39 (45.88)	110 (55.28)	102 (42.32)			
Radiation only	94 (17.9)	22 (25.88)	42 (21.11)	30 (12.45)			
Chemotherapy only	5 (0.95)	0 (0)	0 (0)	5 (2.07)			
Surgery and radiation	86 (16.38)	5 (5.88)	18 (9.05)	63 (26.14)			
Surgery and chemotherapy	3 (0.57)	0 (0)	0 (0)	3 (1.24)			
Radiation and chemotherapy	7 (1.33)	0 (0)	0 (0)	7 (2.9)			
Surgery, radiation, and chemotherapy	6 (1.14)	0 (0)	0 (0)	6 (2.49)			
Active surveillance/No treatment	64 (12.19)	17 (20)	25 (12.56)	22 (9.13)			
Unknown/missing	9 (1.71)	2 (2.35)	4 (2.01)	3 (1.24)			
Vital Status, n (%)					0.294	0.001	0.098
Dead	80 (16.81)	14 (17.07)	18 (9.89)	48 (22.64)			
Alive	396 (83.19)	68 (82.93)	164 (90.11)	164 (77.36)			
Median Follow Up, months (IQR)	53.18 (60.91)	50.86 (71.06)	58.63 (54.83)	50.32 (59.3)			

Grey indicates insufficient sample size for statistical comparison.
^a All sites within head and neck region
^b Includes CN I, II, III, IV, V, VI, VII, IX, X, XI, XII

4 – FACTORS ASSOCIATED WITH SURVIVAL

For benign HNP, single modality surgical excision was associated with 8-fold and 17-fold improved survival relative to single modality radiotherapy and active surveillance respectively. For locally invasive tumors, surgical resection with adjuvant radiation was associated with 3-fold improved survival compared with surgery alone.

Table 3. Multivariate Factors Associated with Overall Survival in HNP

	Benign		Borderline		Locally Invasive	
	n=80		n=160		n=192	
	Overall p<0.0007		Overall p<0.0018		Overall p<0.0001	
Variable	aHR ^a (95% CI)	p	aHR ^a (95% CI)	p	aHR ^a (95% CI)	p
Age (continuous)	1.04 (1-1.08)	.061	1 (0.96-1.05)	0.893		
Age (categorical)					1.00	
< 30 y					4.99 (0.54-46.42)	.158
30-39 y					3.29 (0.37-29.26)	.286
40-49 y					8.49 (0.96-74.77)	.054
50-59 y					11.62 (1.33-101.9)	.027
60-69 y					20.09 (2.15-188.01)	.009
70-79 y					19.43 (1.61-233.84)	.019
≥ 80 y						
Primary Payor					1.00	
Private Insurance			1.00			
Medicare/Medicaid/Other Gov't			4.53 (1.23-16.71)	0.023	1.52 (0.62-3.76)	.360
Not insured					1.85 (0.37-9.21)	.453
Charlson Deyo Score					1.00	
0			1.00			
1			1.67 (0.57-4.89)	0.349		
2			53.45 (9.11-313.77)	<.0001		
3						
Distant metastasis status					1.00	
Negative						
Positive					2.66 (1.18-5.99)	.018
Overall treatment					1.00	
Surgery only	1.00					
Radiation only	8.19 (0.96-70.31)	.055			1.1 (0.36-3.37)	.865
Chemotherapy only					1.31 (0.12-14.02)	.821
Surgery and XRT	19.49 (1.73-219.39)	.016			0.36 (0.12-1.07)	.065
Surgery and chemotherapy					2.69 (0.28-25.47)	.388
XRT and chemotherapy					2.68 (0.53-13.56)	.234
Surgery, XRT, and chemotherapy						
Active surveillance/No treatment	17.03 (1.95-148.42)	.010			2.36 (0.68-8.16)	.174
Margins					1.00	
Negative						
Positive					3.03 (1.07-8.58)	.037

Adjusted for factors with p<0.1 on univariate analysis. Missing hazard ratios indicate insufficient sample size for cox proportional hazards model.

5 – REGIONAL METASTATIC DISEASE

Regional lymph node metastasis was identified in 80.6% of patients who underwent lymph node testing and 43% of patients with locally invasive HNP. About half of patients who underwent lymphadenectomy had five or fewer lymph nodes tested.

Table 4. Analysis of Biopsied Regional Lymph Nodes for Invasive HNP

	Overall	Locally Invasive ^a	RLN Biopsy ^b	Positive RLN ^c	Distant Metastasis ^d
Primary Site of Tumor:	(n=525)	(n=241)	(n=129)	(n=104)	(n=36)
Carotid body	177	177	115	93	23
Intracranial	152	9	0	0	3
Cranial nerves ^e	134	12	0	0	3
Other tumor sites	62	43	14	11	7

RLN: Regional lymph node.
^a Locally Invasive refers to invasive or microinvasive tumors
^b Patients with one or more RLNs examined by pathologist during first course of treatment
^c Patients with one or more positive RLNs confirmed by pathologist during first course of treatment
^d Spread to distant organs or distant lymph nodes at time of diagnosis
^e Includes CN I, II, III, IV, V, VI, VII, IX, X, XI, XII

Table 5. Number of Regional Lymph Nodes Examined

Number of Lymph Nodes:	n (%)
1-5 Nodes	64 (49.6)
6-10 Nodes	22 (17)
11-20 Nodes	13 (10.1)
21-30 Nodes	13 (10.1)
>30 Nodes	8 (6.2)
Unknown number of nodes	9 (7)
Total number of regional lymph nodes that were removed and examined by the pathologist (n = 129).	

6 – CONCLUSION

Clinical Characteristics of Tumor Behavior

- HNP can be divided into phenotypes based on local tumor behavior
- Borderline tumors were more likely to behave like benign tumors than locally invasive tumors
- Locally invasive tumors are more likely than benign or borderline tumors to present with regional or distant metastatic disease

Factors Associated with Survival

- Mortality benefit with surgical resection for benign HNP
- Mortality benefit with surgical resection plus adjuvant radiation for locally invasive HNP
- Unable to control for contrasting patient characteristics or disease course due to limited data available in NCDB

Regional Metastatic Disease

- Regional disease may be underreported for locally invasive HNP due to infrequent or insufficient sampling of regional lymph nodes
- Low chance of distant metastatic spread with regional metastasis

7 – REFERENCES

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