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ORIGINAL ARTICLE

Abdominal Paragangliomas: Analysis of Surgeon's Experience

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ABSTRACT

Abdominal paraganglioma is a rare endocrine tumor associated with genetic mutations, however, the ability to predict long-term risk of metastasis has not been clarified. The aim of this study was to examine the clinicopathological features and outcomes in patients undergoing surgery for an abdominal paraganglioma. A retrospective analysis was performed for all patients undergoing surgery for abdominal paragangliomas from one surgical department between 1998 and 2010. Clinical presentation, hormone secretion and clinical outcomes were examined. A total of 23 patients underwent surgery for abdominal paraganglioma with the most common presentation being hypertension. Median time to metastasis was 32 months with all patients developing disease progression having a rise in urine catecholamines. Patients with capsular invasion or predisposing genetic conditions are at a higher risk of having more aggressive disease. All patients with a diagnosis of paraganglioma should be screened for predisposing genetic abnormalities and postoperative follow-up must include routine urinary catecholamine assessment.

Keywords: Paraganglioma, Neuroendocrine, Catecholamines, Endocrine surgery.

INTRODUCTION

Paragangliomas are rare extra-adrenal catecholamine producing tumors that are found along the sympathetic and parasympathetic chain. Like pheochromocytomas, paragangliomas are frequently associated with familial gene disorders, such as von Hippel-Lindau disease (VHL) or succinate dehydrogenase (SDHD) gene mutations. Metastatic malignant paraganglioma carries a 5-year survival of 20 to 45%,[1] however, histologically, it is difficult to distinguish between benign and malignant paragangliomas with the WHO definition of a malignant paragangliomas being one with metastasis.[2]

This leads to difficulty in giving patients a prognosis following surgery and deciding on the length of follow-up needed. Most case studies to date reporting on paragangliomas have included adrenal pheochromocytoma and head and neck paragangliomas.

The aim of this study is to report on a single surgeon's series of patients undergoing surgery for abdominal paragangliomas with respect to clinicopathological features and outcomes.

MATERIALS AND METHODS

A retrospective analysis of the records of all patients undergoing surgery with abdominal paragangliomas, between March 1998 and 2010 was carried out. The records of 23 consecutive patients undergoing surgery for abdominal paraganglioma were reviewed. All cases were considered as extra-adrenal paragangliomas as there was no connection to the adrenal gland at surgery or on pathological examination. All patients underwent a combination of radiological imaging preoperatively, most commonly a CT, MRI ± MIBG scan preoperatively. Prior to operating, patients were treated with phenoxybenzamine orally with the addition of beta-blockers if needed and perioperatively all patients with a preoperative diagnosis of paraganglioma had a phenoxybenzamine infusion for hypertension control. An analysis was performed of all cases with regard to clinical presentation, intraoperative findings, pathology and clinical follow-up. Information on follow-up for all patients was available from presentation until death or March 2010.

RESULTS

A total of 23 consecutive patients underwent surgery for 24 abdominal paragangliomas between 1998 and 2010. Ages ranged from 16 to 81 at time of diagnosis with a median age of 39.5. The most common presenting features were symptoms related to hypertension, as summarized in Table 1.

Preoperative scanning accurately localized the tumor in all cases. In three patients presenting with an abdominal mass alone, only a CT was performed as they were thought to have a retroperitoneal sarcoma, locally invading uterine tumor and infected intraperitoneal cyst respectively. In those with levels measured preoperatively, 15 had catecholamine secreting tumours while five had normal urinary catecholamines or metabolites. (Table 2).

Most patients had an open operation, six cases were completed laparoscopically while one was converted to a laparotomy, but it is intended that more cases will now be done laparoscopically. There was one perioperative death

(postoperative bleeding), while two patients required ITU admission, both for less than 24 hours. The median length of hospital stay was 6 days (range 1-17).

Median tumor size was 62.5 mm with the largest being 180 × 130 × 50 mm in dimension. The majority of para-aortic tumours were found caudal to the left renal vein (n = 12) (Table 3). Six pathological specimens had evidence of capsular invasion and of these three also had lymphovascular infiltration (LVI) on histological examination.

Metastatic disease occurred in four patients during the follow-up period (median 32 months, range 2-100 months), two of which had a gene mutation. The median time to metastasis was 32 months and three of these patients have since died of their disease. All cases with metastatic disease had raised catecholamines at routine follow-up, which led to further investigation.

Disease-free and overall survival are shown in Figures 1 and 2 respectively and show that the disease-free survival is 68% at 5 years. Of the patients developing metastasis, four in total, three had evidence of capsular invasion on histology. The patient with no capsular or lymphovascular invasion who developed metastasis had a SDHB mutation.

Table 1: Patient characteristics of 23 cases of abdominal paraganglioma including those cases with genetic mutation

Total number of patients	23
Sex (male/female)	11:12
Median age at diagnosis (years)	39.5 (range: 16-81)
Hereditary cases (number):	
– MEN 2A	1
– SDH-B	5
– SDH-D	1
– NF-1	1
Clinical presentation:	
– Hypertension	8
– Abdominal pain/mass	6
– Palpitations/arrhythmia	5
– Screening (known genetic predisposition)	4

Table 2: Pattern of preoperative serum catecholamine/metabolite secretion in the 23 cases of abdominal paraganglioma

Catecholamine secretion	*Patient numbers*
Noradrenaline	2
Noradrenaline/normetadrenaline	5
Noradrenaline/normetadrenaline/ vanillylmandelic acid	8
Nonsecreting	5
Not done	3

Table 3: Tumor characteristics (24 tumors in 23 patients) in relation to size and site

Location		
Cranial to left renal vein	Caudal to left renal vein	Uterine/bladder
10	12	2
Size		
< 50 mm	50-100 mm	> 100 mm
13	8	3

DISCUSSION

Paragangliomas are rare chromaffin cell tumors located at any extra-adrenal site along the sympathetic or parasympathetic nervous system and account for 10 to 20% of chromaffin cell tumors.[3] Abdominal paragangliomas are sympathetic chain derived tumors and found most commonly along the aorta with the majority found in the Zuckerkandl body (the root of the inferior mesenteric artery),[4] although there are reports of unusual clinical sites, such as the kidney,[5] gallbladder[6] and the omentum.[7]

The clinical presentation of abdominal paraganglioma may vary depending on the functional status of the tumor. Catecholamines are converted into inactive metanephrine and normetanephrine by catechol-O-methyltransferase, therefore plasma and urinary metanephrines measurement is superior to catecholamine measurement,[8] but may fail to diagnose solely dopamine secreting tumors or tumors that secrete only small amounts of catecholamines. Common symptoms in relation to catecholamine production include headache, hypertension, weight loss and arrhythmia. In nonfunctioning tumors paragangliomas may present as a mass or with symptoms due to a mass effect. In this study the most common presentation was hypertension related symptoms.

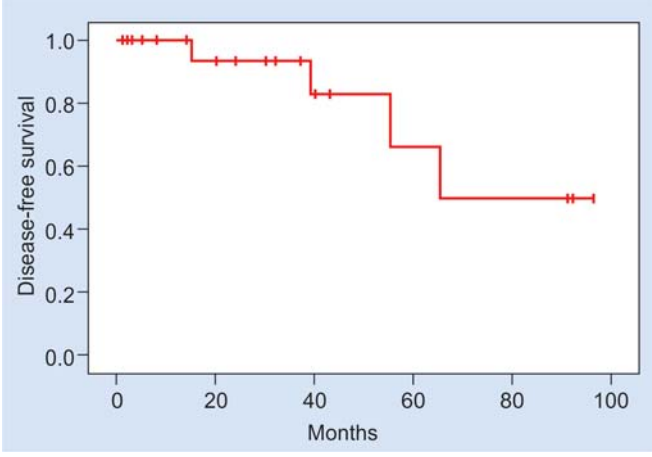

Fig. 1: Disease-free survival for patients with abdominal paraganglioma with a disease-free survival of 68% at 5 years

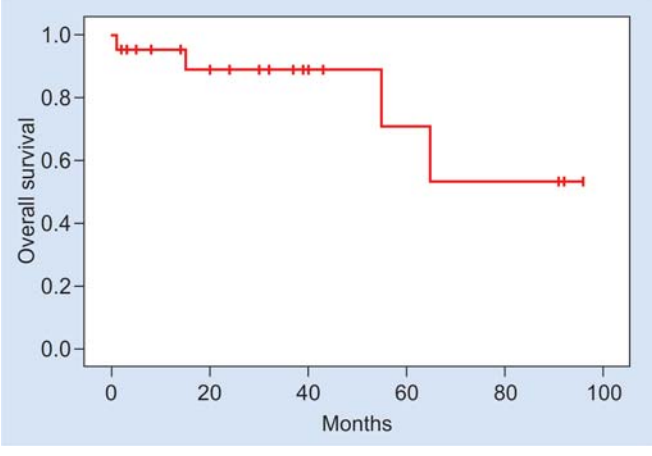

Fig. 2: Overall patient survival following surgery for abdominal paraganglioma showing an overall survival of 70% at 5 years

Patients with elevated catecholamines or its products should undergo radiological imaging to locate the tumor, exclude metastasis and in the case of familial syndrome, look for other neoplasms. CT has a sensitivity of 77 to 98% in identifying paragangliomas measuring more than 1cm, MRI has a higher sensitivity and specificity (90-100% and 50-100% respectively), especially in paragangliomas when compared to phecochromocytomas.[9] Iodine labeled metaiodobenzylguanidine (I-MIBG) scintigraphy works on the basis that the MIBG is transported into chromaffin cells via human norepineprine transporter (hNET), however, it is less sensitive for paraganglioma than pheochromocytoma.[10]

Most paragangliomas are sporadic in nature, but there are genetic conditions associated with an increased incidence of paragangliomas, including multiple endocrine neoplasm type 2 (MEN2–rearranged in transfection (RET) proto-oncogene mutation), von Hippel-Lindau disease (VHL-VHL tumor suppressor gene mutation) and neurofibromatosis type 1 (NF-1–NF 1 tumor suppressor gene mutation). There is also a group of familial paraganglioma syndromes resulting from mutation of the succinate dehydrogenase genes which are also tumor suppressor genes (SDHD, SDHB, SDHC).[11] In cases with SDHB mutations paragangliomas rather than pheochromocytomas are more common and there is an increase in the rate of malignancy of the tumor.[12] In this series, one patient with a SDHB mutation had a histological benign tumor but went on to develop metastasis.

The malignant potential based on histological characteristics alone is still controversial. Metastasis can occur to lymph nodes, bone, liver and lung, and in this series metastasis occurred locally, in lung, liver and bone. Metastasis occurred in three patients who had evidence of capsular invasion on histology, however, further three patients with evidence of capsular invasion on histology have no evidence of recurrent or metastatic disease at a median of 39 months follow-up.

Up to 35% of abdominal paragangliomas are malignant, especially if associated with a SDHB gene mutation.[13] Abdominal paragangliomas are strongly associated with SDHB mutations and increasingly it is recommended that all new diagnoses are tested for the mutation.[14] Overall 39% of the patients who underwent surgery for abdominal paragangliomas in this study had an underlying genetic mutation and of these two developed metastasis with one dying as a result of metastatic disease. One patient with evidence of capsular invasion and SDHB mutation remains disease-free at 32 months follow-up. This patient had postoperative MIBG therapy and remains under close observation.

The main treatment option in cases of abdominal paraganglioma is surgical resection.

Preoperative assessment and management is vital to ensure a smooth perioperative period. Preoperative blockade of alpha-mediated vasoconstriction should occur at least 2 weeks prior to surgery. Beta-blockers may also be used if the patient remains hypertensive. Although the majority of our reported cases were resected in the standard open fashion, more and more reports are of successful resection laparoscopically.[15-17]

In cases of metastatic paraganglioma, the 5-year survival rate is up to 50% and patients with mutations are at a higher risk of developing metastasis, therefore adjuvant treatment following paraganglioma surgery has been investigated. Meta-iodobenzylguanidine (MIBG) is a guanethidine analog that is found in chromaffin storage granules, and uses the same membrane transport as catecholamines (VMA transporters). It can only be used in patients that show a high tumor uptake of scintigraphy on ^{123}I-MIBG or ^{131}I-MIBG scans.

Iodine labeled MIBG (I^{131}MIBG) use was first described in 1983 in the case of a metastatic pheochromocytoma.[18] Since then it has been used in the treatment of high-risk paragangliomas as well as in metastatic disease with tumor response in 24 to 45% of patients.[19] Side effects include, hypothyroidism even with the addition of potassium iodide, mild thrombopenia and leukopenia. Trials are ongoing into improving the uptake and efficacy of MIBG therapy as well as defining the optimum timing and dosage of the treatment. The use of radiolabelled somatostatin analogs may also be beneficial on its own or in combination with MIBG, as somatostatin receptors have been demonstrated on paragangliomas.[20]

Postoperatively urine and plasma metanephrines and catecholamines should be checked annually and, if levels remain elevated, further radiological investigation will be needed to look for metastasis or residual disease. It is now being recommended that all cases of paraganglioma undergo screening for underlying gene mutations.

As paragangliomas have a higher chance of malignancy but as yet no definite pathological markers predict malignancy. It has been recommended that patients with paragangliomas are followed up indefinitely.[21] All the patients presented here, who developed metastasis, had an increase in catecholamines or metabolites having had a normal reading postoperatively.

CONCLUSION

Patients with paragangliomas often present with classical catecholamine related symptoms, but occasionally can present with abdominal pain or a mass. In patients with an underlying genetic mutation the risk of recurrent or metastatic disease is greater even if the histology of the resected specimen is favorable. All patients with a diagnosis of paraganglioma should undergo genetic analysis to detect a previously undiagnosed germline mutation and have undergone long-term follow-up catecholamine biochemical measurements. Those with genetic mutations may then be considered for further therapeutic intervention following their surgery.

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REFERENCES

1. Erickson D, Kudva YC, Ebersold MJ, Thompson GB, Grant CS, van Heerden JA, et al. Benign paragangliomas: Clinical presentation and treatment outcomes in 236 patients. J Clin Endocrinol Metab Nov 2001;86(11):5210-16.
2. Solcia ESLH. Histological typing of endocrine tumours: WHO Classification, International Histological Classification of Tumours. Berlin: Springer 2000.
3. Elder EE, Elder G, Larsson C. Pheochromocytoma and functional paraganglioma syndrome: No longer the 10% tumor. J Surg Oncol Mar 2005;89(3):193-201.
4. Hayes WS, Davidson AJ, Grimley PM, Hartman DS. Extra-adrenal retroperitoneal paraganglioma: Clinical, pathologic, and CT findings. AJR Am J Roentgenol Dec 1990;155(6):1247-50.
5. Rafique M, Bhutta RA, Muzzafar S. Case report: Intra-renal paraganglioma masquerading as a renal cyst. Int Urol Nephrol 2003;35(4):475-78.
6. Miller TA, Weber TR, Appelman HD. Paraganglioma of the gallbladder. Arch Surg Oct 1972;105(4):637-39.
7. Archontovasilis F, Markogiannakis H, Dikoglou C, Drimousis P, Toutouzas KG, Theodorou D, et al. Paraganglioma of the greater omentum: Case report and review of the literature. World J Surg Oncol 2007;5:87.
8. Guller U, Turek J, Eubanks S, Delong ER, Oertli D, Feldman JM. Detecting pheochromocytoma: Defining the most sensitive test. Ann Surg Jan 2006;243(1):102-07.
9. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab Feb 2004;89(2):479-91.
10. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, et al. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. J Clin Oncol Jun 2007;25(16): 2262-69.
11. Baysal BE. On the association of succinate dehydrogenase mutations with hereditary paraganglioma. Trends Endocrinol Metab Dec 2003;14(10):453-59.
12. Tischler AS. Pheochromocytoma and extra-adrenal paraganglioma: Updates. Arch Pathol Lab Med Aug 2008;132(8): 1272-84.
13. Amar L, Baudin E, Burnichon N, Peyrard S, Silvera S, Bertherat J, et al. Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. J Clin Endocrinol Metab Oct 2007;92(10): 3822-28.
14. Benn DE, Richardson AL, Marsh DJ, Robinson BG. Genetic testing in pheochromocytoma and paraganglioma-associated syndromes. Ann NY Acad Sci Aug 2006;1073: 104-11.
15. Brewster JB, Sundaram CP. Laparoscopic resection of an interaortocaval paraganglioma: Diagnosis following a needle biopsy. JSLS Oct-Dec 2007;11(4):502-05.
16. Mithani SK, Marohn MR, Freischlag JA, Dackiw AP, Zeiger MA. Laparoscopic resection of a paraganglioma of the organ of Zuckerkandl in a patient with a carotid body tumor. Am Surg Jan 2006;72(1):55-59.
17. Noda E, Ishikawa T, Maeda K, Inoue T, Amano R, Kubo N, et al. Laparoscopic resection of periadrenal paraganglioma: A report of two cases. Surg Laparosc Endosc Percutan Tech June 2008;18(3):310-14.
18. Sisson JC, Shapiro B, Beierwaltes WH, Glowniak JV, Nakajo M, Mangner TJ, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med Feb 1984;25(2): 197-206.
19. Troncone L, Rufini V. Nuclear medicine therapy of pheochromocytoma and paraganglioma. Q J Nucl Med Dec 1999;43(4):344-55.
20. Van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, et al. Effects of therapy with [177 Lu-DOTA0, Tyr 3] octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. J Nucl Med Oct 2006;47(10):1599-606.
21. Plouin PF, Gimenez-Roqueplo AP. Initial work-up and long-term follow-up in patients with phaeochromocytomas and paragangliomas. Best Pract Res Clin Endocrinol Metab Sep 2006;20(3):421-34.