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Clinical Paper

Recurrence of Phaeochromocytoma and Abdominal Paraganglioma After Initial Surgical Intervention

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ABSTRACT

Background: Clinical and biochemical follow up after surgery for phaeochromocytoma is essential with long term studies demonstrating recurrence frequencies between 6% and 23%.

Aim: To examine the characteristics and frequency of tumour recurrence in a regional endocrine referral centre, in patients with surgical resection of phaeochromocytoma (P) and abdominal paraganglioma (AP).

Methods: We identified a cohort of 52 consecutive patients who attended our Regional Endocrinology & Diabetes Centre and retrospectively reviewed their clinical, biochemical and radiological data (between 2002 and 2013). After confirmation of early post-operative remission by negative biochemical testing, tumour recurrence was defined by demonstration of catecholamine excess with confirmatory imaging.

Results: Phaeochromocytoma was confirmed histologically in all cases (43:P, 9:AP, mean-age:53years). Open adrenalectomy was performed in 20 cases and laparoscopically in 32. Hereditary phaeochromocytoma was confirmed by genetic analysis in 12 (23%) patients. Median follow up time from initial surgery was 47 months, (range: 12 - 296 months), 49 patients had no evidence of tumour recurrence at latest follow-up. Three patients (6%) demonstrated tumour development, one in a patient with VHL which occurred in a contralateral adrenal gland, one sporadic case had local recurrence, and an adrenal tumour occurred in a patient with a SDHB gene mutation who had a previous bladder tumour. After initial surgery, the tumours occurred at 8.6, 12.0 and 17.7 years respectively.

Conclusion: In this study tumour development occurred in 6% of patients. Although tumour rates were low, careful and sustained clinical and biochemical follow up is advocated, as new tumour development or recurrence may occur long after the initial surgery is performed.

Key words: phaeochromocytoma, abdominal paraganglioma, long term follow up, tumour recurrence

ABBREVIATIONS

CST clonidine suppression test
P phaeochromocytoma
AP abdominal paraganglioma
SDHB succinate dehydrogenase complex subunit B
SDHD succinate dehydrogenase complex subunit D
VHL von hippel-lindau
MEN multiple endocrine neoplasia
NF neurofibromatosis
SEM standard error of the mean
IVC inferior vena cava
MIBG metaiodobenzylguanidine scintigraphy
CT Computed tomography
MRI magnetic resonance imaging

INTRODUCTION

Phaeochromocytoma is a rare catecholamine producing tumour that arises from chromaffin cells of the adrenal medulla.[1] Paragangliomas (extra-adrenal phaeochromocytoma) originate from neural crest cells and can occur in locations such as the carotid body, organ of Zuckerlandl, kidney, bladder and in the retroperitoneum.[2,3] Surgical excision of abdominal paraganglioma does not guarantee cure as local recurrence and distant metastases can occur and therefore vigilance is needed in this population.[4,5] Sustained clinical and biochemical follow up after initial surgical resection is essential, the '10 per cent rule' is often

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TABLE 1

Baseline characteristics at presentation

	PHAEOCHROMOCYTOMA n = 43	PARAGANGLIOMA n = 9
Age (at diagnosis; years)	55.2 ± 2.0	41.6 ± 4.9 †
Range	20 – 59	26 – 82
Gender		
Male	16	2
Female	27	7
Mode of Presentation		
Incidentaloma	5	2
Abdominal pain	12	6
Hypertension	24	5
Sweats	15	2
Headache	13	2
Palpitations	14	3
Flushing	3	0
Hypertensive crisis	2	0
Syndromic screening	5	0
Panic attack	3	0
Genetics		
NF1	2	0
SDHB	1	4
SDHD	3	0
VHL	1	0
MEN 2A	1	0
Clonidine Suppression Test		
Positive	32	5
Negative	3	3
Not done	8	1
MIBG		
Positive	22	9
Negative	3	0
Not done	18	0
Location at Presentation		
Left Adrenal	23	
Right Adrenal	19	
Bilateral Adrenal	1	
Abdominal Paraganglioma		9

Data presented as Mean ± SEM, †: p< 0.05

The following criteria were applied to constitute a positive clonidine suppression test using plasma catecholamines: baseline plasma adrenaline and noradrenaline more than 11.82 nmol/l or plasma adrenaline and noradrenaline more than 2.96 nmol/l 3 hrs after administration of clonidine and < 50% fall in noradrenaline 3hrs post clonidine

frequently quoted with regards to phaeochromocytoma recurrence, however the reported rates of recurrence can range from 6 to 23%.[6-8] Furthermore, tumour recurrence can occur many years after the initial surgery, and in some cases can be delayed as long as 10 years to first recurrence.[9,10] Most cases of phaeochromocytoma are sporadic in origin, however in patients with hereditary phaeochromocytoma tumour recurrence is more common, in addition extra-adrenal phaeochromocytoma recur more frequently than adrenal phaeochromocytomas.[11-13]

Against this background we retrospectively examined the characteristics and rate of new tumour development or recurrence over a recent eleven year period at our centre in a cohort of 52 consecutive patients treated by surgical removal of phaeochromocytoma and abdominal paraganglioma.

PATIENTS AND METHODS

The medical records of 52 patients who had surgical resection

of phaeochromocytoma and abdominal paraganglioma and were followed up at the Regional Centre for Endocrinology & Diabetes, Belfast were examined retrospectively between January 2002 and April 2013. Two patients had surgery performed at a different centre. The clinical characteristics of patients were collected as well as biochemical, radiological, surgical and subsequent histological data. All patients were followed up for a minimum period of 12 months after surgical removal of the tumour. Phaeochromocytoma was confirmed by catecholamine excess, confirmatory imaging (CT with contrast as the first choice for localisation, MRI if applicable and/or MIBG scintigraphy) and by subsequent histological analysis. Laparoscopic adrenalectomy as the first line procedure for removal of phaeochromocytoma was introduced at our centre in 1998.[14] After confirmation of initial post-operative negative biochemical testing, tumour recurrence was defined by demonstration of catecholamine excess with confirmatory imaging. All statistical analysis was performed using SPSS software version 20 (SPSS Inc, Chicago). Values are reported as mean ± SEM and the probability value of $p < 0.05$ was deemed significant.

RESULTS

Phaeochromocytoma was confirmed histologically in all cases, 9 of which were abdominal paragangliomas, (male: 18, female: 34, mean age: 53 years, range: 20-82 years). Common clinical presentation included the classic symptoms of headache, palpitations, sweats and hypertension, 7/52 (13%) were discovered incidentally. Two patients with phaeochromocytoma presented with a hypertensive crisis after elective non-related surgical procedures.[15] The location at initial presentation included left adrenal: 23 (44%), right adrenal: 19 (37%), bilateral-adrenal: 1 (2%) and abdominal paraganglioma: 9 (17%). Hereditary phaeochromocytoma as illustrated in Table 1 was confirmed by the presence of classical features of NF-1 in 2 cases and by genetic analysis in a further 10 patients (SDHB: 5, SDHD: 3, VHL: 1, MEN2A: 1), the remaining patients (n=40) were considered to be sporadic in origin. For a variety of reasons four patients did not have measurement of twenty four urine catecholamines before their diagnosis of phaeochromocytoma/paraganglioma:one patient with renal failure requiring dialysis had a positive CST and MIBG scanning pre-operatively. The second patient had surgery performed at a different centre, pre-operative CST was negative. The third patient also had surgery performed at a different centre for a mass adjacent to the IVC/Liver, CST was not performed pre-operatively. The fourth patient had a nephrectomy/adrenalectomy for a renal mass, immunohistochemistry revealed a phaeochromocytoma in the adrenal gland, CST and MIBG were not performed pre-operatively. From the cohort, 27/48 (56%) had raised 24 hr urine adrenaline levels, 21/48 (44%) had raised 24 hr urine noradrenaline levels, 11/48 had both 24 hr elevations in urine noradrenaline and adrenaline levels, one patient had elevated dopamine levels. Clonidine suppression testing was performed in 43 patients, 37 (86%) of which showed a positive response, of the 6 patients with negative clonidine suppression testing we elected to proceed to surgery if urine catecholamines were elevated, and/or MIBG scanning was positive.[16] MIBG scanning was undertaken in 34 patients, 31 (91%) demonstrated positivity. Open adrenalectomy was performed in 20 cases and laparoscopic surgery in 32. The median follow up time was 47 months, (range: 12 - 296 months), 49 patients in the remaining cohort had no evidence of new tumour development or recurrence on follow up. After initial surgery, three patients (6%) demonstrated the presence of tumour development; one with Von Hippel Lindau syndrome (VHL), another with a sporadic phaeochromocytoma and one with a SDHB mutation. Contra-lateral adrenal tumour developed in one patient with VHL, in another with presumed sporadic phaeochromocytoma local tumour was present (in this patient a regional lymph node was inaccessible on initial surgery), the third patient with an SDHB mutation developed tumour growth in an adrenal gland, the original site of which was the bladder. After initial surgery tumour development occurred at 8.6, 12 and 17.7 years respectively, two of these patients were alive at most recent follow up at 19 & 25 years respectively. In the third patient with VHL syndrome, death was not related to phaeochromocytoma. Overall 46/52 patients were alive at most recent follow up, 1 death was attributable to metastatic paraganglioma, 20 months after initial surgery.

TABLE 2

Surgical and histological data

	PHAEOCHROMOCYTOMA n = 43	PARAGANGLIOMA n = 9
Surgical Procedure		
Open Adrenalectomy	12	8
Laparoscopic Adrenalectomy	31	1
Specimen Weight (grams)	140.9 ± 47.2	113.6 ± 68.6
Range	8.5 - 1861	1.5 - 620
Specimen Size Length (cm)	4.2 ± 1.0	4.6 ± 0.42
Range	1.5 - 19.0	2.2 - 13.0

Data presented as Mean ± SEM

DISCUSSION

Surgical removal of a phaeochromocytoma and abdominal paraganglioma can be difficult due in part to its anatomical location and thus surgery does not automatically confer a cure and, therefore both immediate and long-term assessments are essential.[17] In addition paragangliomas can present difficulties by appearing in unusual and surgically inaccessible locations resulting in incomplete tumour resection or tumour spillage.[18] Most centres now perform laparoscopic adrenalectomy as the preferred choice. However, tumour size and location necessitate open adrenalectomy in selected cases.[19-21] Laparoscopic resection has been deemed feasible even in patients who have a large (>6cm) phaeochromocytoma, provided there is a low suspicion for malignancy.[22] Caution should be advised, as increased rates of adrenal recurrence have been demonstrated in laparoscopic in comparison to an open procedure.[17] In our own previous series of adrenalectomies (8 of 50 for phaeochromocytoma) and in keeping with other similar studies, laparoscopic adrenalectomy in comparison to open adrenalectomy resulted in a significantly shorter hospital stay and less post-operative morbidity, although operating time was longer.[14] Some centres have reported varying degrees of success with cortical sparing adrenalectomy, more so in patients with bilateral phaeochromocytoma but it is not our current practice to perform this procedure.[23,24]

If recurrence does occur surgical removal is the first line treatment. In the current study we have demonstrated tumour development in 6% in patients in whom phaeochromocytoma and abdominal parganglioma had been surgically removed, it is arguable that genuine local recurrence in our study occurred in only one patient, in the remaining two patients who had tumour development after initial surgery; one with VHL and the other with an SDHB mutation, could possibly be explained by the increased clinical incidence of bilateral phaeochromocytomas (around 40-60%) in patients with VHL, and that patients with SDHB mutations have an increased risk of the development of multi-focal phaeochromocytomas.[25-27]

Our study numbers are comparable to previous cohorts investigating rates of recurrence in phaeochromocytoma.[3,27,28] Our current practice in Northern Ireland enables us to follow the majority of these patients long term at one centre. Previously we have reported a recurrence rate of 15% at a median interval of 5 years, a possible reason for the low recurrence rate in the current study was the relatively short follow up time,[8] we therefore presume that if patients were followed up for a longer time period, further tumour development or recurrences would possibly occur. In the current study the time to first recurrence ranged from 8.6 to 17.7 years, this demonstrates the value of prolonged follow up even in those patients who appear to have been surgically cured.

All patients with an initial surgical resection of phaeochromocytoma or abdominal paraganglioma should be followed up with careful history, examination and routine measurements of catecholamines, if the latter are raised, further imaging (initially CT with contrast) is recommended. Recent clinical practice guidelines have provided evidence for the superiority of plasma free or urinary fractionated metanephrines in comparison to measurements of catecholamines in the diagnosis of phaeochromocytoma and paraganglioma.[29] Previously published studies addressing the risk factors for recurrence demonstrate an increased risk in younger patients, larger tumours, extra-adrenal in origin and in those with genetic phaeochromocytoma.[30,31] In this regard, predicting which patients might recur in the current study was difficult, given the relatively low numbers. Current guidelines suggest that all patients with a phaeochromocytoma should be followed by for at least 10 years after surgery and in those patients with an extra-adrenal tumour or genetic phaeochromocytoma should be followed lifelong. [32]

CONCLUSION

Although tumour development and recurrence rates were low after initial surgery, careful sustained clinical and biochemical follow up is advocated, as tumour occurrence may occur long after the initial surgery.

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