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ORIGINAL ARTICLE

Postoperative Outcomes of Familial Adrenal Pheochromocytoma

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ABSTRACT

There are no current guidelines for the management of familial pheochromocytoma (FP). We tried to determine the optimal management of patients with FP. Among 191 patients with pheochromocytoma who underwent surgical resection between 1979 and 2010, there were 18 FP (13 different kindreds; 11 females/7 males; mean age at initial operation: 38.7 years). The 18 FP cases comprised 10 with MEN2A, 2 with MEN2B, 4 with von Hippel-Lindau disease, and 2 with FP only, and all pheochromocytomas were of adrenal origin. The number of probands and family members was 9 and 9 respectively. Mean tumor size was 6.4 cm in diameter. Simultaneous bilateral adrenalectomy was performed in 6 patients, and unilateral adrenalectomy was performed as the initial surgery in 12 patients. A metachronous contralateral adrenalectomy was performed in 3 patients, 90, 236 and 312 months after the primary operation, respectively. None of the patients received partial adrenalectomy. Among another 9 patients with unilateral adrenalectomy, contralateral pheochromocytomas were suspected in 4 cases at the initial operation. However, none of these contralateral lesions developed severe symptoms or tumor enlargement during a median follow-up of 116 months. In the remaining 5 patients, pheochromocytoma did not develop in the contralateral adrenals over a median follow-up of 80.5 months. Bilateral lesions of adrenal pheochromocytoma in familial cases occurred in 78% of cases (14/18); 9 patients (including 4 with contralateral pheochromocytoma) did not require a contralateral adrenalectomy during a median follow-up of 119 months. No patients have suffered from Addisonian crisis. The ipsilateral adrenalectomy and follow-up of contralateral small pheochromocytoma is one of the management options to preserve adrenocortical function in FP patients.

Keywords: Pheochromocytoma, Management, Familial pheochromocytoma, Hereditary pheochromocytoma, Bilateral adrenal pheochromocytoma.

INTRODUCTION

Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. The clinical manifestations of pheochromocytoma such as hypertension, tachycardia, pallor, headache, and feelings of panic or anxiety are induced by the direct actions of excess catecholamine secretion. Acute hypertensive attack due to pheochromocytoma can cause sudden death mainly as a result of encephalopathy, a cerebrovascular accident or neurogenic pulmonary edema. Once the diagnosis of pheochromocytoma is made, the treatment of choice is surgical removal of the tumor.

The clinical characteristic of pheochromocytoma has been expressed as a 10% tumor. Roughly, 10% of pheochromocytomas have been considered familial, however, it is now recognized that germline mutations are found as frequently as 32% of pheochromocytomas and paragangliomas, after the identification of the SDH-related mutations.[1] Familial pheochromocytoma (FP) classically constitutes a component of multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), and, rarely, neurofibromatosis type 1.[2] Almost all patients with MEN2 and the majority with VHL have pheochromocytomas of adrenal origin and benign tumors, whereas patients with SDHx mutations have extra-adrenal pheochromocytomas (paragangliomas) and a high incidence of malignant tumors. The management of FP is different between classic FP, such as MEN2 or VHL, and newly categorized SDHx paragangliomas.

FP patients have a potential to develop bilateral adrenal pheochromocytoma and the surgical management of FP is still controversial. Prophylactic total adrenalectomy is never performed because it commits the patient to lifelong steroid hormone replacement and the risk of Addisonian crisis. Partial adrenalectomy, so-called 'cortical sparing adrenalectomy', has been proposed for the treatment of bilateral adrenal pheochromocytoma and to maintain adrenocortical function.[3] However, the long-term outcomes of partial adrenalectomy in patients with FP are not evident so far.

In the last 31 years, we have performed bilateral total adrenalectomy for patients with bilateral large pheochromocytoma or unilateral total adrenalectomy for patients with or without small tumors in the contralateral adrenal gland. In this study, we reviewed the long-term outcomes of unilateral or bilateral total adrenalectomy for FP and tried to determine the optimal management of patients with FP.

PATIENTS AND METHODS

From January 1979 through December 2010, a total of 191 patients underwent adrenal surgery for a diagnosis of pheochromocytoma at the Department of Breast and Endocrine Surgery, Nagoya University Hospital. Among 191 patients with pheochromocytoma, 18 FP in 13 kindred were identified (female 11, male 7, median age at initial operation: 37 years; range: 20-73 years). We defined FP as a patient with more than two family members with pheochromocytoma among second-degree relatives. The number of probands and family members was 9 and 9, respectively (the median age at the initial operation: probands 35 years, family members 37 years). The 18 FP patients comprised 10 with MEN2A, 2 with MEN2B and 4 with VHL. The other 2 patients with bilateral pheochromocytoma had a familial history of pheochromocytoma but did not meet criteria of any known syndromes, such as MEN, VHL or NF1. All 18 pheochromocytomas were of adrenal origin. Genetic studies were performed in 9 cases with informed consent and the permission of the ethical committee. Patient demographics are shown in Table 1.

According to the sequence of adrenalectomy and the current adrenal status, 18 patients were divided into the following subgroups: (1) Group A: simultaneous bilateral adrenalectomy, (2) Group B: metachronous bilateral adrenalectomy, (3) Group C: unilateral adrenalectomy with suspected contralateral lesion, (4) Group D: unilateral adrenalectomy with no contralateral lesion. Laparoscopic adrenalectomy was performed in 6 recent cases with unilateral lesion. The average tumor size was 3.7 cm in diameter in laparoscopic procedures. None of the patients had partial adrenalectomy either by open or laparoscopic surgery. The patients were followed up to December 2010 by patient visits, correspondence, phone calls or physicians' letters. No patients were lost to follow-up.

RESULTS

A simultaneous bilateral adrenalectomy was performed in 6 patients (Fig. 1, Group A). One patient died of metastatic medullary thyroid carcinoma one year after adrenalectomy without pheochromocytoma recurrence. One patient required left completion total adrenalectomy for recurrent pheochromocytoma after right total adrenalectomy and left subtotal adrenalectomy 396 months later. The recurrent pheochromocytoma weighed 850 gm and measured 16 cm in diameter. The other 4 patients have not shown any symptoms or laboratory examinations for suspecting pheochromocytoma recurrence (Table 2).

Unilateral total adrenalectomy was performed as the initial surgery in 12 patients with FP. A metachronous contralateral adrenalectomy was performed in 3 patients, 90, 236 and 312 months after the primary operation, respectively (Group B). Contralateral pheochromocytomas developed over 5 cm in diameter clinical symptoms were apparent in two patients in Group B, 20 years or more after primary surgery. The third patient in Group B had a small adrenal tumor in the contralateral side and no symptoms with low urinary catecholamine levels. Laparoscopic left total adrenalectomy was performed 7.5 years after primary right adrenalectomy because the patient wanted to have a child. The patient delivered a baby safely under careful corticosteroid replacement 3 years after the completion adrenalectomy. In 4 patients with unilateral adrenalectomy, contralateral pheochromocytomas were suspected at the initial operation. However, none of these contralateral lesions developed severe symptoms or tumor enlargement during follow-up of 51, 114, 118 and 179 months (Group C). In 5 patients, pheochromocytoma did not develop in the contralateral adrenals over a median follow-up of 101 months (Group D). One patient died from repeated cerebral infarction at the age of 72, 204 months after primary surgery.

The changes in urinary catecholamine levels before and after unilateral adrenalectomy are shown in Figure 2. Urinary catecholamine levels were reduced in patients after unilateral adrenalectomy and remain at low levels even in patients with small contralateral adrenal enlargement (Group C).

Table 1: Patient demographics

Family-Patient No.	*Sex*	*Age**	*Proband or family*	*Type of disease*	*Mutation*
I-1	F	28	Proband	MEN2A	Cys618Arg
II-1	F	25	Family	MEN2A	Cys634Arg
III-1	F	40	Proband	VHL	N/D
IV-1	M	28	Proband	N/A	N/D
V-1	M	55	Family	MEN2A	N/D
VI-1	F	22	Proband	MEN2A	Cys634Gly
VII-1	M	20	Proband	VHL	N/D
VIII-1	M	52	Proband	MEN2A	Cys634Ser
IX-1	M	56	Proband	MEN2B	Met918Thr
VII-2	M	24	Family	VHL	N/D
V-2	F	40	Family	MEN2A	N/D
X-1	F	73	Proband	MEN2A	N/D
I-2	F	37	Family	MEN2A	Cys618Arg
III-2	F	35	Family	VHL	N/D
XI-1	F	35	Proband	MEN2B	Met918Thr
XII-1	M	53	Family	N/A	N/D
XIII-1	F	37	Family	MEN2A	Cys634Arg
VI-2	F	37	Family	MEN2A	Cys634Gly

Age *: Age at initial surgery; N/A: Not applicable; N/D: Not determined.

Consequently, life-long steroid replacement therapy is necessary in 9 patients with bilateral total adrenalectomy, while normal adrenocortical function after unilateral adrenalectomy in another 9 patients with FP. None of the patients has suffered from acute adrenal insufficiency.

At last follow-up, 14 out of 16 patients were alive at a median follow-up of 157 months (range, 7 to 515 months) after initial adrenalectomy. Median follow- up after the latest surgery was 128 months. None of the patients exhibited malignant pheochromocytoma.

DISCUSSION

In our series, bilateral lesions of adrenal pheochromocytoma in FP occurred in 72% of cases (13/18). Both in MEN2 (8/12) and VHL (3/4), about 70% of patients had bilateral adrenal pheochromocytomas. We have performed simultaneous bilateral adrenalectomy only for the patients with FP who have gross tumor (> 4 cm) of both adrenals. The decision to perform unilateral or bilateral adrenalectomy was based on adrenal appearance on CT or MRI and MIBG uptake. Simultaneous bilateral total adrenalectomy was reserved only for patients with pheochromocytoma larger than 4 cm in diameter and bilateral strong uptakes in MIBG scintigraphy. Nine patients were at risk for adrenal insufficiency as a result of having undergone bilateral adrenalectomy either concurrently for synchronous disease or separately after development of recurrent contralateral pheochromocytoma. None of the patients has suffered from acute adrenal insufficiency. To avoid fatal complications from Addisonian crisis, our management includes education not only for the patient but also family members concerning the importance of taking medications daily, and possession of an emergency card stating that the patient received bilateral total adrenalectomy. We have performed bilateral total adrenalectomy in many patients with Cushing disease before

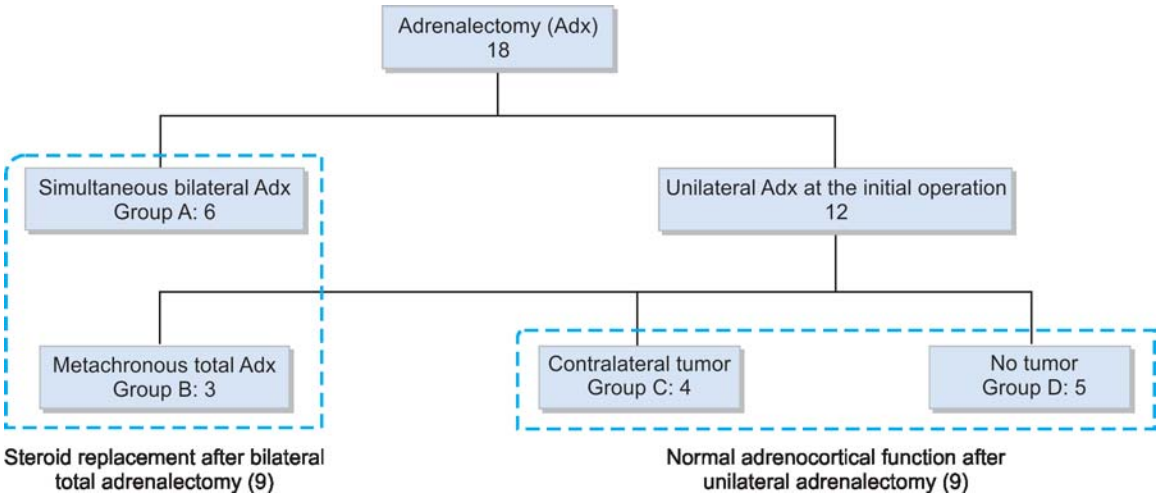

Fig .1: Sequence of adrenalectomy (Adx) and current states of adrenal function in the patients with familial pheochromocytoma

Table 2: Tumor characteristics and follow-up

Family- Patient No.	*Tumor size (cm)*		*Group*	*Type of surgery*	*Months between surgery*	*Prognosis*
	Right	*Left*				
I-1	6	7	B	Metachronous	312	Alive
II-1	17	16	A	Simultaneous	396[#]	Alive
III-1	4	10	A	Simultaneous		Alive
IV-1	12	9	A	Simultaneous		Alive
V-1	3	N	D	Unilateral		Dead
VI-1	10	2	B	Metachronous	90	Alive
VII-1	3[*]	5	C	Unilateral		Alive
VIII-1	4	4	A	Simultaneous		Dead
IX-1	N	6	D	Unilateral		Alive
VII-2	7	3[*]	C	Unilateral		Alive
V-2	11	3[*]	C	Unilateral		Alive
X-1	N	6	D	Unilateral		Alive
I-2	3	2[*]	C	Unilateral		Alive
III-2	3	N	D	Unilateral		Alive
XI-1	7	5	A	Simultaneous		Alive
XII-1	5	9	A	Simultaneous		Alive
XIII-1	5	5	B	Metachronous	236	Alive
VI-2	2	N	D	Unilateral		Alive

N: No adrenal tumor
[*]: Contralateral small pheochromocytomas have been followed without surgical intervention
[#]: Left completion total adrenalectomy was performed 396 months after right total adrenalectomy and left subtotal adrenalectomy.

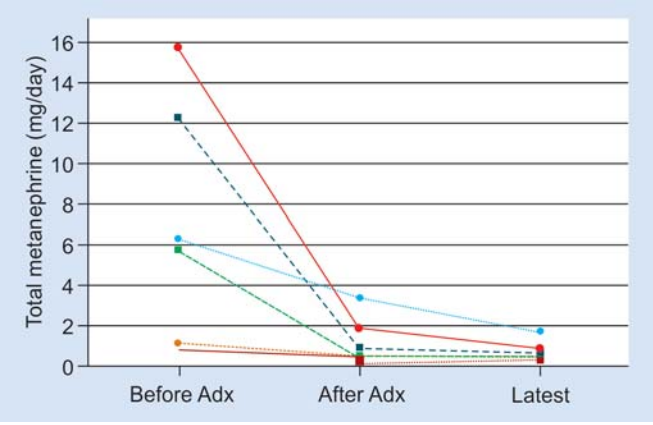

Fig. 2: Changes in urinary total metanephrine levels were available in 7 patients with unilateral adrenalectomy. Urinary total metanephrine levels were decreased after unilateral adrenalectomy in all these 7 patients, and remain low even in the patients with small adrenal tumor in the contralateral adrenal gland in Group C. Open circles represent the values in patients with Group C, and open squares represent the ones in patients with Group D

the advent of the Hardy's operation in the 1960s and 1970s.[4] In Japan, all citizens are covered by national insurance system in which universal free access to healthcare services is afforded to everybody.[5] This system of easy access to hospital services for any Japanese patient may play an important role in the patient avoiding Addisonian crisis. However, all patients with total bilateral adrenalectomy are not always guaranteed protection by this type of system. Therefore, we should avoid as much as possible placing patients in possible Addisonian crisis.

Unilateral total adrenalectomy was performed as the initial surgery in 12 patients with FP, and 3 received contralateral adrenalectomy (Group B, Table 2). Two patients had 5 cm or larger pheochromocytomas 236 and 312 months after primary surgery, respectively. Both patients had several symptoms of catecholamine excess. The other patient of Group B (second surgery for desired pregnancy) and 4 patients of Group C had a small adrenal tumor in the contralateral side and showed no symptoms with low urinary catecholamine levels (Fig. 2) at a median follow-up of 152 months (range, 89 to 220 months). Rodriguez et al reported the same policy in patients with pheochromocytoma in MEN2A.[6]

Partial adrenalectomy, so-called 'cortical sparing adrenalectomy', has been proposed for the treatment of bilateral adrenal pheochromocytoma and to maintain adrenocortical function.[3] Lee et al carried out partial adrenalectomy using an open transabdominal approach in 14 patients with MEN2 and VHL, and 13 patients (93%) had normal postoperative cortisol levels and were weaned off replacement therapy. Recurrent pheochromocytomas developed in three patients (21%), and nine other patients were alive without recurrent tumor at a mean 90 months of follow-up.[7] Asari et al reported that 5 (38%) of 13 patients in adrenal-sparing adrenalectomy developed recurrence in the contralateral gland.[8] Recurrences of pheochromocytoma are inevitable in patients with FP after partial adrenalectomy since it is impossible to remove the entire medulla while keeping the cortex. Moreover, adrenomedullary chromaffin cells are found in all zones of the adult adrenal cortex.[9] The indication for partial adrenalectomy is a pheochromocytoma less than 3 cm in diameter. Adrenal tumors including pheochromocytoma have a potential of malignancy, which has been proven by reported disseminated recurrence of adrenal tumor after laparoscopic adrenalectomy.[10] We are anxious to disperse pheochromocytoma cells during the dissection of the adrenal gland using ultrasonic coagulator. We have not performed partial adrenalectomy but just follow-up without surgical intervention in patients with small pheochromocytoma of FP because the majority of pheochromocytomas are benign and usually have a silent function. Hopefully, future molecular studies will allow us to better define genotype: phenotype relationships in familial pheochromocytoma patients so as to properly select those that can be observed *vs* those at higher risk for developing bilateral disease at a young age.

CONCLUSION

Ipsilateral adrenalectomy and follow-up of contralateral small pheochromocytomas are one management option to preserve adrenocortical function in FP patients, although this is based on a very small number of patients and needs further clarification.

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