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단일기관에서의 양측성갈색세포종에서 부신부분절제수술의 경험 : 임상결과와 유전자 분석

Clinical Outcomes and Genetic Analysis of Partial Adrenalectomy in Bilateral Pheochromocytoma: A Single-Institute Experience

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Abstract

Clinical Outcomes and Genetic Analysis of Partial Adrenalectomy in Bilateral Pheochromocytoma: A Single-Institute Experience

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Background: The use of partial adrenalectomy in the management of bilateral pheochromocytoma to maintain normal adrenal function is emerging, but there are concern about tumor recurrence due to remained adrenal tissue. Bilateral pheochromocytoma is frequently associated with hereditary disease; therefore, it is important to perform a genetic test to identify hereditary tumor syndrome for the patient

and their relatives. Moreover, there is a need for studies that compare the clinical outcomes of total versus partial adrenalectomy with long-term efficacy. Herein, we aimed to determine the clinical outcomes and genetic testing results for partial adrenalectomy and total adrenalectomy in patients with bilateral pheochromocytoma.

Methods: We retrospectively reviewed the medical records of patients with bilateral pheochromocytoma treated at Seoul National University Hospital from January 1998 to August 2020. Twenty-six patients who underwent bilateral adrenal surgeries were divided into the partial adrenalectomy group, with at least a unilateral side, and the bilateral total adrenalectomy group. Genetic mutation results were obtained by direct sequencing or using the Next-generation sequencing technique. Clinical outcomes including adrenal function and tumor recurrence and the results of genetic analyses were investigated.

Results: Among 26 patients, 23 underwent partial adrenalectomy and 3 underwent bilateral total adrenalectomy. Nineteen patients (73.1%) had mutations: 12 patients (46.2%) had *RET* mutations, 4 (15.4%) had *VHL* mutations, and 3 (11.5%) had *SDHD* mutations. Six (23.1%) patients had no mutation. Mean tumor size was larger in the total adrenalectomy group than in the partial adrenalectomy group (6.3±3.3 cm vs. 5.1±1.7 cm, p=0.395). Three patients (13.0%) in the partial adrenalectomy group required steroid hormone supplement therapy and all patients (100%) in the total adrenalectomy group become steroid

dependent (p=0.008). Four patients (17.4%) in the partial adrenalectomy group and 1 patient (33.3%) in the total adrenalectomy group had tumor recurrence (p=0.488).

Conclusion: Partial adrenalectomy prevent the need for chronic steroid hormone replacement therapy in most of the patients and the recurrence risk appears low. Therefore, partial adrenalectomy can be a safe and feasible option for patients with bilateral pheochromocytoma.

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Keywords: Bilateral pheochromocytoma; Partial adrenalectomy; Total adrenalectomy; Minimally invasive adrenal surgery

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I. Introduction

Pheochromocytoma is a rare adrenal tumor that produces catecholamines. It arises from chromaffin cells of the adrenal medulla. The commonly associated symptoms include headaches, palpitations, and profuse sweating [1]. The estimated incidence of pheochromocytoma is approximately 0.6 per 100,000 person-years in the general population. A recent study reported an incidence of 0.18 per 100,000 person-years in South Korea, but the incidence surges up to 0.2-0.6% in patients with hypertension in outpatient clinics [2]. Pheochromocytoma often occurs sporadically, but up to 40% of pheochromocytoma cases are hereditary, and 3-11% of all patients have bilateral pheochromocytoma [3]. Bilateral or multifocal pheochromocytoma is often discovered in syndromic diseases, including mutations of *RET* (rearranged during transfection). This consequently leads to multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau (VHL) syndrome, or neurofibromatosis type 1 (NF1) as well as familial paraganglioma syndromes type 1 (SDHD, succinate dehydrogenase complex subunit D), type 2 (SDHAF2, succinate dehydrogenase complex assembly factor 2), type 3 (SDHC, succinate dehydrogenase complex subunit C), type 4 (SDHB, succinate dehydrogenase complex subunit B), and type 5 (SDHA, succinate dehydrogenase complex subunit A). In addition, other different susceptibility genes have been associated with the pathogenesis of bilateral pheochromocytoma [4, 5]. Therefore, when patients present with bilateral pheochromocytoma, they should be referred for genetic

testing and genetic counselling because it is known that such diseases often occur in the heritable tumor syndrome [6]. Next-generation sequencing (NGS) is now considered a suitable method for performing the diagnosis of genetic diseases; this method is reported to have increased accuracy and reveals information of genetic variants. By performing molecular genetic testing in the context of genetic counseling using the NGS technique, clinicians can make a differential diagnosis among several hereditary diseases to create a tailored optimal management strategy and provide appropriate care and surveillance for the patient and their relatives [7, 8].

Surgical resection is the treatment of choice in pheochromocytoma, but conventional radical removal of adrenal glands by bilateral total adrenalectomy in bilateral adrenal disease could lead to adrenal insufficiency. The use of partial adrenalectomy for treating patients with bilateral pheochromocytoma has gained popularity owing to advances in organ-preserving surgery; this approach has a comparable surgical outcome and perioperative complications [9]. The 2014 Endocrine Society clinical practice guideline recommend partial adrenalectomy for hereditary or bilateral pheochromocytoma [10]. Even though the surgical management of pheochromocytoma has improved, partial adrenalectomy has not been adopted as the gold standard treatment for bilateral pheochromocytoma because there have always been concerns about recurrence from the residual adrenal tissue and the comparative difficulty in the surgical techniques than total adrenalectomy can increase surgical complications. Contrary to total

adrenalectomy, which can cause surgical complications, including the need for lifelong steroid replacement therapy, partial adrenalectomy preserves the normal adrenal tissue with meticulous dissection of tumors to decrease the risk of steroid dependency, which can cause osteoporosis, hypoandrogenism, diabetes mellitus (DM) and Addisonian crisis [11, 12]. However, this operation should be considered with the risk of pheochromocytoma recurrence from the residual adrenal tissue. Therefore, the treatment strategy of bilateral adrenal involvement of pheochromocytoma should be carefully considered to provide the optimal treatment with a focus on preserving normal adrenal function and excising the adrenal tumor completely. Therefore, studies elucidating the clinical outcomes of partial adrenalectomy and its long-term efficacy are crucial.

The present study aimed to provide comprehensive information of the genetic analysis results of bilateral pheochromocytomas and the clinical outcomes of partial versus total adrenalectomy in patients with bilateral pheochromocytomas to determine the feasible approach.

II. Methods

Data collection

This was a single-center retrospective study. Data were collected from Seoul National University Hospital between January 1998 and August 2020. A total of 26 patients who underwent bilateral adrenal surgery for

pheochromocytoma were included in this study and were analyzed for the clinical outcomes mentioned earlier (Figure 1). Patients were divided into the partial adrenal surgery group, at least on a unilateral side, and the bilateral total adrenal surgery group on the basis of the operating method. We defined synchronous pheochromocytoma as contralateral pheochromocytoma occurring within 6 months of the initial diagnosis of pheochromocytoma. We also defined metachronous pheochromocytoma as contralateral pheochromocytoma developed more than 6 months after the initial adrenal surgery. Data were retrospectively collected from medical records, which included data on age, sex, tumor size and side, surgery type (total or partial adrenal surgery), surgical approach (open or laparoscopic approach), postoperative complications (steroid replacement and Addisonian crisis), tumor recurrence, histopathology, and results of molecular genetic analysis. Follow-up data were obtained by the endocrinologists or endocrine surgeons. In accordance with the approval obtained from the Institutional Review Board (IRB Number 2008-052-1147), all patients provided signed written informed consent for studies on genetic analysis and clinical outcomes.

Techniques of partial adrenalectomy

Partial adrenalectomy is more difficult and challenging to perform than conventional total adrenalectomy. Several key steps should be considered in partial adrenalectomy when compared to total adrenalectomy, including the surgical extent of the adrenal gland, preservation of the adrenal vein, bleeding control of the transected adrenal gland, and manipulation of the adrenal tumor. First, regarding the surgical extent of the adrenal gland, inspection and palpation of the adrenal tumor are critical to delineate the surgical plane between

the adrenal tumor and the normal adrenal tissue. The surgeon preserves an adequate amount of normal adrenal tissue in partial adrenalectomy, which is sufficient to maintain normal adrenal function; however, the operator is required to resect the adrenal tumor completely. Second, the preservation of the adrenal vein for hormonal drainage from the preserved adrenal tissue is another crucial concern in partial adrenalectomy. Preserving the adrenal vein can reduce the risk of bleeding and maintain hormonal drainage from the preserved adrenal tissue because adrenal vein ligation could induce residual adrenal gland congestion. However, there are conflicting reports regarding the need for preservation of the adrenal vein. In several previous studies, there was no significant difference in steroid hormone dependence between the adrenal vein preservation group and the adrenal vein ligation group [13–15]. Third, hemostasis of the cut surface of the preserved adrenal gland is another important issue because the adrenal glands are small but highly vascular. Transecting the adrenal gland with an energy device is useful for hemostasis, and further hemostasis can be achieved by electrocautery or clipping. Fourth, regarding tumor manipulation, tumor spillage may occur during surgery, which increases the risk of recurrence and causes sudden increased release of catecholamines while manipulating the adrenal tumor. Therefore, meticulous dissection and tumor manipulation are important steps to prevent the rupture of the tumor cell capsule or hemodynamic instability during partial adrenalectomy.

Indications of operative technique

Adrenalectomy can be performed either by the open technique or by the minimally invasive approach. In the present study, minimally invasive surgeries were performed whenever it was possible. Open laparotomy was performed when the tumor was large (>6 cm), had invasive feature, or was located at a site that was not suitable for laparoscopic surgery, or when the patient had a history of previous abdominal operation. We also tried to perform partial adrenalectomy to maintain normal adrenal function when the patients had hereditary pheochromocytomas and bilateral tumors or had a previous history of contralateral adrenalectomy. On the contrary, we performed total adrenalectomy if the tumor was too large to identify normal adrenal tissue or if the adrenal tumors showed invasive features or if there were multiple tumors in one adrenal gland.

Genetic analysis

To confirm diagnosis in patients with a clinical diagnosis of hereditary pheochromocytoma, all patients were offered molecular genetic testing and genetic counseling for pheochromocytoma susceptibility genes. Genetic analysis enables the detection of related cancers in hereditary syndromes and genetic assessments of patients and their relatives for surveillance and screening at-risk patients.

The results of genetic mutation analysis for pheochromocytoma susceptibility genes were reviewed. Genetic mutation testing was conducted by Sanger sequencing only for the *RET, VHL, SDHD*, and

SDHB genes before 2014. However, in 2014, our institution adopted the NGS technique, which is an improved methodology that can capture a broader range of detectable mutations to 10 genes (*MAX, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, TMEM127,* and *VHL*). If the patients had negative results in genetic testing, then the patients were classified in the no mutation group.

Perioperative steroid hormone replacement

Patients who were planned for bilateral adrenalectomy may need lifelong steroid supplementation according to the extent of adrenalectomy. To prevent adrenal insufficiency after bilateral adrenalectomy, they received perioperative steroid hormone replacement therapy according to a standardized protocol followed in our institution.

All patients received 100 mg of intravenous hydrocortisone before simultaneous bilateral adrenalectomy or one remaining unilateral adrenalectomy, followed by 50 mg of intravenous hydrocortisone every 12 hours for 1 day, and the patients received 25 mg of intravenous hydrocortisone every 8 hours for 1-2 days. Moreover, the patients maintained an oral dose of 20-mg and 10-mg hydrocortisone twice daily until the first visit to the outpatient clinic. On the contrary, those with a sufficient amount of residual normal adrenal tissue after partial adrenalectomy can usually have dose tapering of all steroids within 6 months to 1 year. All of the patients underwent repeated biochemical testing to check for hormone secretion function of the hypothalamic-pituitary axis before tapering off the steroid therapy.

Postoperative outcome measurement

Recurrence of pheochromocytoma was defined as biochemical evidence associated with a positive adrenal structural image ipsilateral to the surgery or pathologic study reports during follow-up. Postoperation, steroid hormone supplement therapy was administrated after bilateral total adrenalectomy or if clinical signs of adrenal insufficiency developed after partial adrenalectomy. To assess adrenocortical function, serum cortisol and adrenocorticotropic hormone (ACTH) levels were measured between 6 a.m. and 8 a.m. on the first postoperative day. In patients who received steroid administration before adrenalectomy, blood samples were collected for laboratory tests before the administration of the morning dose. When the patients needed to be assessed regarding whether or not they had adrenal insufficiency, blood samples were collected for analysis of cortisol levels before as well as 30 and 60 min after the administration of ACTH. Addisonian crisis was defined as acute hypotension, marked abdominal symptom, and laboratory abnormalities, requiring immediate correction [16].

Statistics

Statistical analysis was performed using SPSS software for Windows, version 25 (Statistical Software, IBM Corp., Chicago, IL, USA). The difference between groups was analyzed using Mann-Whitney U test. All statistical tests were two-sided, and p-values <0.05 were

considered statistically significant.

III. Results

Clinical characteristics

A total of 26 patients had bilateral pheochromocytoma (Supplementary Table 1). Of these patients, 14 (53.8%) were female and 12 (46.2%) were male. Mean patient age at diagnosis of the first pheochromocytoma was 38.7 years (standard deviation [SD]: 11.2). Table 1 shows patient characteristics, including the results of genetic testing. Of the total 26 patients with bilateral pheochromocytoma at first presentation, 21 (80.8%) had synchronous bilateral pheochromocytoma and 5 (19.2%) had metachronous bilateral pheochromocytoma (Table 2). Twenty-three (88.5%) patients underwent unilateral or bilateral partial adrenalectomy and the remaining 3 (11.5%) patients underwent bilateral total adrenalectomy with subsequent operation on both sides or simultaneously. Bilateral laparoscopic surgery was performed for 8 (30.8%) patients, and open laparotomy was performed for 18 (69.2%) patients, who underwent unilateral laparoscopic adrenalectomy with contralateral open adrenalectomy or bilateral open adrenalectomy. Six (6/8, 75%) patients underwent laparoscopic surgery using the laparoscopic transabdominal anterior approach and 2 (2/6, 25.0%) underwent the posterior retroperitoneoscopic approach.

Candidate gene mutation analysis

Among the total 26 patients, 8 underwent genetic testing with NGS, but the other patients were tested with direct sequencing only for suspected gene mutation lines including *RET, VHL, SDHD*, or *SDHB*. Even after 2014, when our institution adopted NGS, we have continued to run direct sequencing for highly suspected patients with *MEN, VHL*, or *SDHD* mutations. Nineteen patients were found to have genetic mutation in genetic analyses (11 patients with MEN2A; 1, MEN2B; 4, VHL; and 3, SDHD); for 6 patients, the results of genetic analyses showed no mutation (five patients had no mutation in NGS and the remaining patient was tested only for *VHL* and *RET*, which showed no mutation). One patient who refused to undergo genetic testing was classified as unknown in our study, but the patient was strongly suspected for MEN2A because the patient was diagnosed with medullary thyroid carcinoma simultaneously.

In genetic testing, 12 (12/26, 46.2%) patients were found to have 6 germ-line mutations in *RET*, and the majority of *RET* mutations were associated with MEN2A or 2B. Four (4/26, 15.4%) patients had three different mutations in *VHL*, and 3 patients (3/26, 11.5%) had 3 different distinct mutations in *SDHD*. Six (6/26, 23.1%) patients had no mutation in genetic testing, and 1 patient refused to receive genetic counseling or molecular testing (Table 3).

Surgical outcomes

All patients had a follow-up for a median duration of 10 years (130.0 ± 95.4 months). During follow-up, 4 (4/23, 17.4%) patients in the partial adrenalectomy group and 1 (1/3, 33.3%) patient in the total adrenalectomy group had recurrence of pheochromocytoma. Mean tumor size was larger in the total adrenalectomy group than in the partial adrenalectomy group (6.3 ± 3.3 cm vs. 5.1 ± 1.7 cm, p=0.395). Tumor recurrence was managed with active surveillance if the patients were asymptomatic or by reoperation if the patients had significantly elevated levels of catecholamines or developed symptoms of recurrence of a catecholamine-producing tumor. In this study, all patients with recurrence underwent reoperation. Two patients had recurrence at the operation site, and 3 patients had recurrence at another site (one patient had recurrence at the right retrocaval area and another patient had recurrence at the left paraganglioma, last patient recurred between right kidney and IVC right border). Both patients who had recurrence at the operation site were partial adrenalectomy group. One patient also had distane metastasis to lung and the pateint underwent operation for lung either. Most patients (4 out of 5 patients) who had surgery for recurrence underwent resection of the recurred tumor through the open laparotomy approach. Among them, 1 underwent repeated operation through the minimally invasive approach. Mean time to recurrence in the partial adrenalectomy and total adrenalectomy groups was 158.5 (SD: 80.1) months and 149 months after previous surgery, respectively (Table 4). After this surgery, they did not have

another recurrence (follow-up duration was 145 months, 100 months, 94 months, 10 months, and 8 months, respectively).

Postoperative steroid replacement therapy was necessary for 3 (3/23, 13.0%) out of 23 patients who underwent partial adrenalectomy, whereas long-term steroid replacement therapy was necessary for all 3 (100%) patients who underwent total adrenalectomy. Mean age of patients who became steroid dependent in the partial adrenalectomy and total adrenalectomy groups was 46.3 and 39.3 years, respectively. Each patient group was treated with mean hydrocortisone doses of 18.3 and 25 mg, respectively, and the mean duration of steroid supplement therapy was 52.6 and 33.6 months, respectively. There was no Addisonian crisis in both groups. During steroid supplement therapy, 2 patients developed side effects of long-term steroid supplement therapy. One out of 2 patients developed osteoporosis, and the other patient had DM during follow-up. No mortality was observed in this study.

IV. Discussion

Patients with hereditary forms of pheochromocytoma are commonly associated with the development of bilateral and multifocal pheochromocytoma [17]. Previous studies on bilateral pheochromocytoma have focused mostly on inherited syndrome including MEN2, *VHL*, and *SDHD* mutations. Because of the different

natural disease course between familial and sporadic pheochromocytomas, many recent studies have noted these differences in the presentation of hereditary disease [18, 19]. Patients who have hereditary catecholamine-secreting tumors are diagnosed at a younger age, show earlier symptomatic tumor development, have smaller tumors, and experience organ damage before diagnosis because of active biochemical surveillance and genetic testing compared to sporadic tumors [8, 20]. Therefore, genetic testing can be a great approach to the early diagnosis of syndromic hereditary disease and could lead to active surveillance and identification of tumors with effective treatment including prophylactic surgery.

Compared with studies that have used the conventional Sanger sequencing technique based on limited mutations including the *RET, VHL, SDHD,* or *SDHB*, we started using targeted 10-gene panel testing to detect rare genetic variants and improve the diagnostic value. Except for 1 patient who refused to undergo genetic testing, all patients in our group were offered molecular genetic analyses together with genetic counseling to detect predisposing genetic mutations. As expected, most patients (19/26, 73.1%) with bilateral pheochromocytoma in this study had a genetic mutation. Of the 19 patients, 13 (13/19, 68.4%) had a familial history of hereditary tumor syndrome and 7 were diagnosed with bilateral pheochromocytoma from 3 probands in this study group. These patients could have a diagnosis owing to active surveillance, such as genetic testing and genetic counseling initiated from their probands. The observed data can explain that

individual approaches with molecular genetic testing and genetic counseling can help in detecting hereditary tumors at an earlier stage and making gene-informed treatment strategies, leading to the decision of extent of resection in patients who have a high possibility of a future contralateral disease [21]. Therefore, the findings of our study support the recommendation that all patients who have bilateral pheochromocytoma should undergo genetic testing [8, 10, 22].

As reported in previous literature, the increased risk of recurrence is one of the issues in partial adrenalectomy [11]. However, in our series, we noticed fewer recurrence cases in the partial adrenalectomy group than in the total adrenalectomy group (17.4% and 33.3%, respectively). It can be expected that there will be fewer recurrences in the total adrenalectomy group, but in fact, the surgeries were performed in a group of patients with more advanced and large tumors; and hence, it was difficult to preserve normal adrenal tissue. So, there may be a selection bias. Moreover, time to recurrence was shorter than that in the patient group who had undergone partial resection. The small number of cases in the total adrenalectomy group might be one of the reasons for the relatively higher rates of recurrence.

In the aspects of adrenal insufficiency after adrenalectomy, in our study, there was no Addisonian crisis and a small number of patients (13.0%) in the partial adrenalectomy group needed steroid hormone supplementation. In fact, some patients in the present study were in the process of dose tapering of steroid supplements; those patients will not need steroid replacement therapy after long-term follow-up;

therefore, we assumed that the number of patients in the partial adrenalectomy group who needed steroid treatment will decrease. This fact suggests the notion that adrenal insufficiency is greatly reduced in patients undergoing partial adrenalectomy.

According to previous reports, although a patient undergoes unilateral total adrenalectomy, they might have transient or even persistent impairment of adrenocortical function. The patient might have a decreased adrenocortical reserve, which makes it difficult to compensate for the resection of the unilateral adrenal gland compared to that in patients with normal bilateral adrenal glands [21, 22]. In these cases, the risk of developing adrenal insufficiency is increased, requiring steroid hormone supplementation therapy [23]. Therefore, partial adrenalectomy is good option for preserving normal adrenal function in cases with a single small adrenal tumor in one adrenal gland in whom the function of the contralateral adrenal gland is not sufficient.

Several studies have demonstrated clinical outcomes of partial adrenalectomy in patients with bilateral pheochromocytoma (Table 5). Castinetti et al. [12] reported the surgical outcomes of pheochromocytoma associated with MEN2 in patients who underwent partial adrenalectomy. Thirty-five (43%) of 82 patients with bilateral pheochromocytoma have become steroid dependent at final follow-up, and 4 (5%) of 82 patients had recurrence of pheochromocytoma after partial adrenalectomy (mean time to recurrence: 9.5 years [SD: 3.1 years]). Gomella et al. [24] reported that among 107 patients, 10 (9.3%)

became steroid dependent at the time of last follow-up and 17 (15.8%) had local recurrence after partial adrenalectomy (median time to recurrence: 71 months). In a recent meta-analysis, Nagaraja et al. [9] reported low overall recurrence rate (8%, 95% CI: 0.05-0.12) and steroid independent rate (85%, 95% CI: 0.78-0.9) after partial adrenalectomy. Kaye et al. [25] performed a review of 22 studies and demonstrated that the rate of recurrence was only at 3% and more than 90% for patients who avoided lifelong steroid replacement.

The surgeon preserves a sufficient amount of vascularized adrenal gland that will be enough to preserve normal adrenal function in partial adrenalectomy, as opposed to bilateral total adrenalectomy; this minimizes the risk of steroid dependency, which can cause osteoporosis, DM, and Addisonian crisis [13]. Brauckhoff et al. reported that 15-30% of normal adrenal tissue should be preserved to maintain normal adrenal function for glucocorticoid and mineralocorticoid secretion after partial adrenalectomy [26]. Additionally, it increases the risk of developing recurrence because it is impossible to ensure that there is no residual adrenal tumor [27]. Deciding the surgical plane between the adrenal tumor and the normal adrenal gland through laparoscopic and manual palpation is important in partial adrenalectomy. Therefore, it should be performed at specialized centers by experienced surgeons having adequate experience in treating rare bilateral pheochromocytomas [13]. Metastasis of the pheochromocytoma and tumor recurrence because of tumor spillage during surgery constitute some other important concerns [28-30].

Deciding the surgical technique of adrenalectomy is crucial, especially for patients with bilateral pheochromocytoma, for adequate hormone production by preserving adrenal gland function and for avoiding the need for long-term steroid replacement therapy and the possibility of recurrence. Indeed, steroid replacement therapy is unavoidable after bilateral total adrenalectomy. There is also a need for dose adjustment during stressful events owing to loss of response function to stress situations by the adrenal gland. Furthermore, the lifelong use of steroid hormone induces several adverse effects, including Addisonian crisis, osteoporosis, and DM. Addisonian crisis, which is a potentially life-threatening condition, can occur in up to 10-35% of patients who undergo total adrenalectomy on both sides despite proper steroid replacement therapy [31]. Adrenal insufficiency can also occur after unilateral adrenalectomy, which was followed by severe adrenal stress with systematic issues [32]. Therefore, the risk of recurrence has to be weighed against the risks of long-term steroid hormone replacement therapy after partial adrenalectomy.

However, this study had several limitations. This study did not have a systematically proposed model, i.e., a retrospective study design in our single-institute series with a small sample size, and patients were followed up for a median duration of 10 years. Therefore, there continues to be a demand for prospective randomized studies in a large multicenter comparing long-term outcomes between total adrenalectomy and partial adrenalectomy in bilateral adrenal disease.

In conclusion, in the present study, partial adrenalectomy reduced the

need for lifelong steroid hormone replacement therapy in most patients, and resulted in a low risk of recurrence in the residual adrenal tissue. Although the small number of patients in this present study does not allow drawing definitive conclusions about the assessment of risk of adrenal insufficiency and recurrence, we believe that our results along with those of previous studies suggest that partial adrenalectomy is a safe and feasible option in terms of organ preservation in hereditary or sporadic bilateral pheochromocytoma. This study may be useful by providing baseline data for further studies, which would help determine the long-term outcome and efficacy of partial adrenalectomy in patients with bilateral pheochromocytoma.

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Table 1. Patient characteristics (n=26)

Variables	Numbers (n=26)
Age (at first diagnosis, years)	38.7 ± 11.2 (mean ± sd)
Gender (Male : Female)	12 : 14
Genetic analysis technique	
Direct Sequencing	17 (65.4%)
10 gene panel	8 (30.8%)
Not done	1 (3.8%)
Results of genetic testing	
MEN 2A	11 (42.3%)
MEN 2B	1 (3.8%)
VHL	4 (15.4%)
SDHD	3 (11.5%)
No mutation	6 (23.1%)
Unknown	1 (3.8%)

MEN 2A, multiple endocrine neoplasia type 2A; MEN 2B, multiple endocrine neoplasia type 2B; VHL, Von Hippel-Lindau; SDHD, succinate dehydrogenase complex subunit D

Table 2. Operative details of patients with bilateral pheochromocytoma (n=26)

Variables	**Numbers (n=26)**
Bilaterality	
Synchronous pheochromocytoma	21 (80.8 %)
Metachronous pheochromocytoma	5 (19.2 %)
Operation	
Partial adrenalectomy at least a unilateral side	23 (88.5 %)
Bilateral total adrenalectomy	3 (11.5 %)
Type of surgery	
Laparoscopic surgery	8 (30.8%)
Lateral Transperitoneal Adrenalectomy	6 (75.0 %)
Posterior Retroperitoneoscopic Adrenalectomy	2 (25.0 %)
Open laparotomy surgery	18 (69.2 %)

Table 3. Candidate gene mutation analysis

Mutated gene	Variation	Protein change	Numbers (n=26)
RET			12 (46.2%)
	c.1891G>T, p.Asp631Tyr	D631Y	4 (33.3%)
	c.1900T>C, p.Cys634Arg	C634R	4 (33.3%)
	c.2753T>C, p.Met918Thr	M918T	1 (8.3%)
	c.1902C>G, p.Cys634Trp	C634W	1 (8.3%)
	c.1901G>A, p.Cys934Tyr	C634Y	1 (8.3%)
	c.1901G>C, p.Cys634Ser	C634S	1 (8.3%)
VHL			4 (15.4%)
	c.253C>T; 255G>T, p.Leu85Phe	-	2 (50.0%)
	c.278G>A, p.Gly93Asp	G93D	1 (25.0%)
	c.470C>T, p.Thr157Ile	T157I	1 (25.0%)
SDHD			3 (11.5%)
	c.112C>T, p.Arg38*	R38*	1 (33.3%)
	c.327del, p.Val110Leufs*25	-	1 (33.3%)
	c.94_95delTC, p.Ala33Ilefs*35	-	1 (33.3%)

No mutation	No mutation	No	6 (23.1%)
Unknown	Unknown	-	1 (3.8%)

RET, rearranged during transfection; *VHL*, Von Hippel-Lindau; *SDHD*, succinate dehydrogenase complex subunit D

Table 4. Postoperative outcomes of bilateral pheochromocytoma patients

Postoperative outcomes	**Partial adrenalectomy (n=23)**	**Bilateral total adrenalectomy (n=3)**	**P value**
Tumor size	5.1 ± 1.7 (cm)	6.3 ± 3.3 (cm)	P = 0.395
Mean follow-up duration	135.0 ± 91.7 (months)	95.3 ± 138.3 (months)	P = 0.395
Mean time to recurrence	158.5 ± 80.1 (months)	149 (months)	-
Recurrence	4 (17.4%)	1 (33.3%)	P = 0.488
Steroid replacement	3 (13.0%)	3 (100.0%)	P = 0.008
Addisonian crisis	0 (0%)	0 (0%)	-

Table 5. Literature review of surgical outcomes of partial adrenalectomy for pheochromocytoma

Author	Year	No. of patients	Diagnosis	Surgical approach	Surgical extent	Site	Recurrence	Mean time to recurrence	Steroid dependence	Addisonian crisis	Follow up duration, mo	Publication country of origin
Lee et al.	1996	14	MEN2, VHL	Open	Partial, Total (14:1)	Bilateral	3/14 (21%)	206±106 mo	1/14 (7.1%), 1/1 (100%)	0	138 (7-331)	USA
Walz et al.	2006	24	MEN2, VHL, PGL, NF1, sporadic, etc.	Laparoscopi, retroperitoneoscopic	Partial, Total (23:1)	Bilateral	0/24 (0%)	-	2/24 (14.3%)	NR	39.2(8-115)mo	Germany
Benhammou et al.	2010	26	VHL	Open, laparoscopic	Partial	Unilateral, Bilateral	3/26 (11%)	18(1-41)yr	3/26(11%)	NR	9.3 (5-46)yr	USA
Alesina et al.	2011	66	MEN2, VHL, PGL, NF1, sporadic, etc.	laparoscopic	Partial	Bilateral	9/66 (13.6%)	9±10.6yr	6/66(9%)	NR	48 (3-183) mo	Germany
Castinetti et al.	2014	339	MEN2	Open, laparoscopic	Partial, Total (82:257)	Bilateral	4/82 (5%), NR	9.5±3.1yr, NR	35/82 (43%), 257/257 (100%)	NR	NR	France
Neumann et al.	2019	625	MEN2, VHL, NF1, PGL, sporadic, etc.	Open, laparoscopic	Partial, Total (248:377)	Bilateral	33/248 (13.3%), 2/377 (0.5%)	8(4-17)yr, 17(9-25)yr	0, 377/377 (100%)	0, 67/377 (17.7%)	7yr (3-13), 10yr (4-22)	Germany
Gomella et al.	2020	107	MEN2A, VHL, sporadic	Open, laparoscopic, robotic	Partial	Bilateral	17/107 (15.8%)	71 (26-127)	10/107 (9.3%)		60 (13-131)	USA

MEN2, multiple endocrine neoplasia type 2; VHL, Von Hippel-Lindau syndrome; PGL, paraganglioma syndrome; SDHD, succinate dehydrogenase complex subunit D, NF1, Neurofibromatosis type 1;

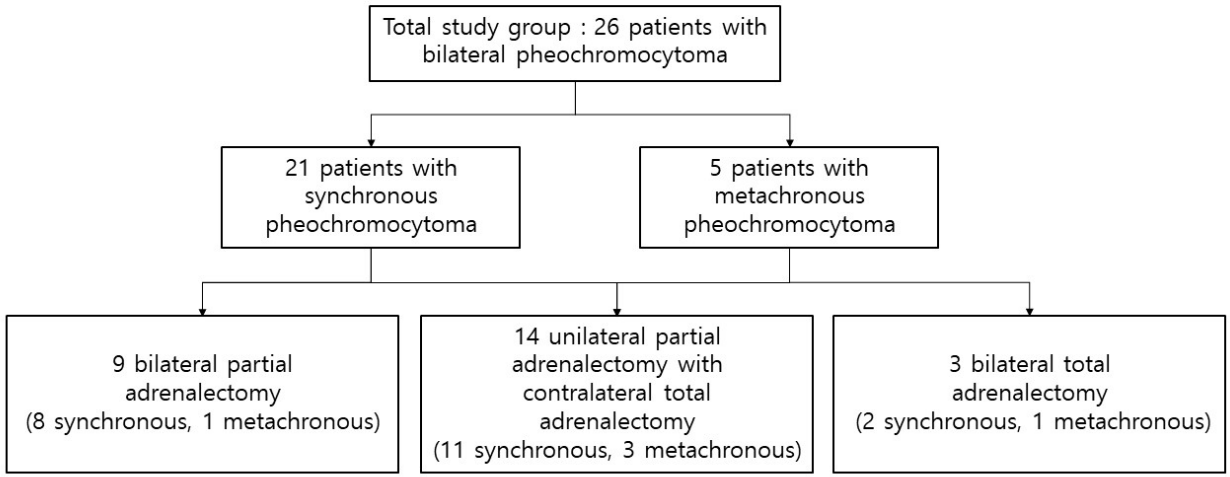
Supplementary table 1. Patients with bilateral pheochromocytoma

Patient	Diagnosis	Mutation	Age	Gender	Operation	Follow-up duration, mo	Steroid dependancy	Hydrocortisone dose, mg (daily)	Complication associated with steroid use	Recurrence	Time to recurrence, mo	Addisonian crisis
1	MEN2A	D631Y	59	F	Unilateral partial	135	No	0	No	No	0	No
2	MEN2A	C634W	49	F	Unilateral partial	140	No	0	No	No	0	No
3	MEN2A	D631Y	49	M	Unilateral partial	131	Yes	15	Osteopenia	No	0	No
4	MEN2B	M918T	24	F	Bilateral total	255	Yes	25	Osteopenia, DM	Yes	149	No
5	MEN2A	C634R	47	M	Unilateral partial	236	No	0	No	No	0	No
6	MEN2A	C634R	40	F	Unilateral partial	282	No	0	No	Yes	125	No
7	MEN2A	C634R	33	F	Bilateral partial	243	No	0	No	No	0	No
8	VHL	G93D	41	M	Unilateral partial	110	No	0	No	No	0	No
9	VHL	L85F	20	M	Unilateral partial	98	No	0	No	No	0	No
10	SDHD	"c.94_95 del TC, p.Ala33Ilefs*35"	48	M	Bilateral partial	163	No	0	No	No	0	No
11	r/o MEN2A	not done	24	M	Bilateral partial	206	No	0	No	No	0	No

12	Sporadic	no mutation	37	F	Unilateral partial	84	No	0	No	No	4	No
13	Sporadic	no mutation	45	F	Unilateral partial	173	No	0	No	Yes	61	No
14	Sporadic	no mutation	35	F	Bilateral partial	41	No	0	No	No	0	No
15	VHL	T157I	23	M	Unilateral partial	38	Yes	10	No	No	0	No
16	VHL	L85F	58	M	Unilateral partial	32	No	0	No	No	0	No
17	SDHD	R38*	48	M	Bilateral partial	30	No	0	No	No	0	No
18	MEN2A	D631Y	48	M	Unilateral partial	26	No	0	No	No	0	No
19	MEN2A	C634S	44	F	Unilateral partial	290	Yes	30	Osteoporosis	No	264	No
20	MEN2A	C634R	33	F	Bilateral partial	243	No	0	No	Yes	221	No
21	Sporadic	no mutation	32	F	Bilateral partial	247	No	0	No	Yes	227	No
22	Sporadic	no mutation	48	F	Bilateral total	19	Yes	20	No	No	0	No
23	MEN2A	D631Y	30	M	Unilateral partial	130	No	0	No	No	113	No
24	Sporadic	no mutation	37	F	Bilateral partial	14	No	0	No	No	0	No
25	SDHD	c.327del, p.Val110 Leufs*25, heterozyg	19	M	Bilateral partial	13	No	0	No	No	0	No

		ote										
26	MEN2A	C634Y	34	F	Bilateral total	12	Yes	30	No	No	0	No

Figure 1. Study population



국문초록

단일기관에서의 양측성갈색세포종에서 부신부분절제수술의 경험 : 임상결과와 유전자 분석

배경: 부신부분절제수술은 양측성갈색세포종의 치료에 있어서 부신 기능을 보존하기 위해 떠오르고 있는 수술법이다. 하지만 부신부분절제수술은 잔존 부신조직으로 인해 재발의 위험을 증가시킬 수 있다. 그리고 양측성갈색세포종의 경우 유전 질환과 연관된 경우가 많기 때문에 환자와 환자의 가족에서 유전성 종양 증후군을 찾아내기 위해 유전자 검사를 시행하는 것이 중요하다. 따라서, 본 연구에서는 양측성갈색세포종 환자에서 부신부분절제수술과 부신전절제수술 환자군에서 임상적 결과와 유전자 검사 결과를 분석하였다.

방법: 서울대학교병원에서 1998년 1월부터 2020년 8월까지 양측성갈색세포종으로 치료받은 환자들의 의무기록을 후향적으로 분석하였다. 26명의 양층성갈색세포종으로 수술 받은 환자를 최소한 한쪽이라도 부신부분절제수술을 받은 환자군과 양측모두 부신전절제수술을 받은 환자군으로 구분하였다. 유전자 돌연변이 결과는 직접염기서열분석법 또는 차세대염기서열분석법을 통해 검사하였다. 부신 기능, 재발 그리고 유전자분석 결과를 포함한 임상 결과를 분석하였다.

결과: 총 26명의 환자 중, 23명의 환자에서 부신부분절제수술을 시행하였고 3명의 환자에서 부신전절제수술을 시행하였다. 19명의 환자(73.1%)에서 돌연변이가 발견됐다. 12 명(46.2%)의 환자에서 *RET*, 4명(15.4%)의 환자에서 *VHL*, 3명(11.5%)의 환자에서 *SDHD* 의 돌연변이가 있었고 6명 (23.1%)에서는 돌연변이가 발견되지 않았다. 종양의 크기의 평균은 부

신전절제수술 환자군이 부신부분절제수술 환자군 보다 더 큰 것으로 나타났다(6.3 ± 3.3 cm vs 5.1 ± 1.7 cm, p=0.395). 부신부분절제수술 환자군에서는 3명(13.0%)의 환자에서 스테로이드 호르몬 보충이 필요했고, 부신전절제수술 환자군에서는 모든 환자(100%)에서 스테로이드 호르몬 보충이 필요했다(p=0.008). 부신부분절제수술 환자군에서는 4명(17.4%)의 환자에서 재발하였으며 부신전절제수술 환자군에서는 한 명(33.3%)의 환자에서 재발하였다(p=0.488).

결론: 부신부분절제수술은 대부분의 환자에서 만성적인 스테로이드 호르몬 보충요법의 필요를 감소시켰으며 재발의 위험도 낮은 것으로 나타났다. 따라서, 부신부분절제수술은 양측성갈색세포종 환자에서 안전하고 실현 가능한 치료법이다.

주요어 : 양측성갈색세포종, 부신부분절제수술, 부신전절제수술, 최소침습부신수술
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