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

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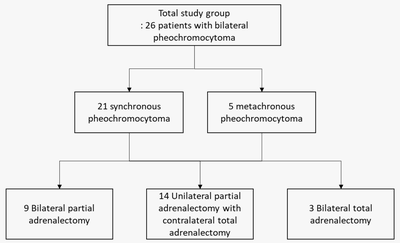
Background

- Partial adrenalectomy is emerging in the management of bilateral pheochromocytoma to preserve adrenal function, but it can increase the risk of recurrence due to residual adrenal tissue.
- And bilateral pheochromocytoma is associated with hereditary disease, so it is important to get a genetic evaluation to detect hereditary tumor syndrome for the patient and their relatives.
- Herein, we described clinical outcomes and results of genetic testing between partial adrenalectomy and total adrenalectomy groups in bilateral pheochromocytoma.

Materials and Methods

- **Patients**
  - From January 1998 to August 2020
  - 26 patients were treated with subset analysis of adrenal function and recurrence between total adrenalectomy and partial adrenalectomy group

- **Figure 1. Patient population**



- **Genetic analysis**
  - To confirm the diagnosis for patients whose clinical diagnoses are hereditary pheochromocytoma
    - All patients were offered molecular genetic testing and genetic counseling for pheochromocytoma susceptibility genes
  - Sanger sequencing for RET, VHL, SDHD, SDHB before 2014
  - 10-gene panel for pheochrmocytoma/PPG after 2014 (MAX, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, TMEM127, VHL)
  - With genetic counseling

- **Retrospectively reviewed**
  - Patient characteristics
  - Type of surgery (total or cortical sparing adrenalectomy)
  - Surgical approach (open or laparoscopic approach)
  - Postoperative complications
  - Adrenal insufficiency, Addisonian crisis, steroid supplement
  - Recurrence
  - Histopathology
  - Results of molecular genetic analysis

Results

- **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%)

- 19 patients (68.4%) were found to have mutations
- 12 patients had mutations of RET (46.1%), 4 of VHL (15.4%), 3 of SDHD (11.5%) and 6 patients showed no mutation (23.1%)
- The results of genetic testing were not obtained from 1 patient (3.8%)

- **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 %)

- Of the 26 patients, 23 patients (88.5%) underwent partial adrenalectomy and 3 patients (11.5%) underwent bilateral total adrenalectomy

- **Table 3. Results of genetic testing**

Mutated gene	Variation	Protein change	Numbers (n=26)
RET			12 (46.1%)
	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.1901G>A, p.Cys634Tyr	C634Y	1 (8.3%)
	c.1902C>G, p.Cys634Trp	C634W	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%)

- **Table 4. Postoperative outcomes of bilateral pheochromocytoma**

Postoperative outcome	Partial adrenalectomy (n=23)	Bilateral total adrenalectomy (n=3)	P value
Tumor size (cm)	5.1 ± 1.7	6.3 ± 3.3	P = 0.329
Mean follow-up duration (months)	135.0 ± 91.7	95.3 ± 138.3	P = 0.509
Mean time to recurrence (months)	158.5 ± 80.1	149	P = 0.922
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%)	-

- Mean tumor size was larger in total adrenalectomy compare to partial adrenalectomy group (6.3 ± 3.3 cm vs 5.1 ± 1.7 cm, p=0.329)
- Three patients (13.0%) required steroid hormone supplement therapy in partial adrenalectomy group and all patients (100%) in total adrenalectomy group become steroid dependent
- There were 4 recurred patients (17.4%) in partial adrenalectomy group and 1 recurrence (33.3%) in total adrenalectomy group

Discussion

- Individual approaches with molecular genetic results and genetic counseling can help to detect hereditary tumors and to make gene-informed treatment strategies, leading to the decision of adrenal preserving surgery in patients who have a high possibility of future contralateral disease.
- The Addisonian crisis which is potentially life-threatening condition can occur in up to 10%-35% of patients who undergo both sided total adrenalectomy, despite proper steroid replacement.
- In our study, Partial adrenalectomy prevented the need for chronic steroid hormone supplement therapy in the majority of patients (82.6 % of patients)
- The risk of recurrent pheochromocytoma in remnant adrenal gland treated with partial adrenalectomy technique was low (17.4% of patients)

Conclusion

- Partial adrenalectomy can be a safe and feasible option in terms of organ-preserving surgery in hereditary or sporadic bilateral pheochromocytoma

References

1. *Lenders, J.W. et al., Lancet. 2005; 366: 665–675*
2. *Neumann, H.P. et al., Endocr Relat Cancer. 2008; 25, T201–T219*
3. *Alesina, P.F. et al., Langenbecks Arch Surg 2012; 397:233–238*