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Case Report

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Synchronous Bilateral Retroperitoneoscopic Cortical Sparring Adrenalectomies - Case Series and Literature Review

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Introduction

Cortical-sparing synchronous bilateral adrenalectomy is one of the rarest operations performed because it is limited to a very small subset of patients with bilateral pheochromocytomas or ACTH-dependent Cushing's syndrome non-amendable to first-line treatments.

Pheochromocytomas occur bilaterally in 3-11% of all patients and up to 60% of patients with hereditary syndromes such as Von Hippel-Lindau (VHL) disease and Multiple Endocrine Neoplasia 2 (MEN2) [1-2]. Hence, treatment inevitably involves removal of both adrenal glands [3]. Favourable data supporting cortical sparing bilateral adrenalectomy for bilateral hereditary pheochromocytomas was first reported in 1996 [4], and current guidelines continue to support this approach to prevent permanent hypocortisolism [5].

The other indication for bilateral adrenalectomy is for Cushing's disease. Surgical resection is recommended as first line treatment options for bilateral adrenal disorders such as ACTH-independent macronodular adrenal hyperplasia and primary pigmented nodular adrenal disease. It is the second-line treatment option for ACTH-dependent Cushing's syndrome when there is failure of medical therapy, radiotherapy, or trans-sphenoidal surgery, or if surgery was not possible. It is also recommended as emergency treatment in patients with very severe ACTH-dependent disease who cannot be promptly controlled by medical therapy [6].

There are a few approaches to adrenalectomy. The current gold standard is laparoscopic via either a posterior retroperitoneal (Walz) approach or lateral transabdominal / transperitoneal (Gagner) approach [7]. The former is preferred for patients requiring bilateral adrenalectomy or had previous abdominal surgery, while the latter allows for evaluation of intra-abdominal cavity and offers more space for dissect of larger tumours. Open adrenalectomy can be considered if visual control of the anatomical area is needed in complex oncological cases. However, open bilateral adrenalectomy has historically been associated with high complication rates [8]. This has translated into 83% (1555/2073) of all adrenal cases in the United Kingdom from 2010 to 2015 being performed laparoscopically, with only a 4.6% conversion rate [9]. Robotic adrenalectomy and laparoscopic single-site surgery (LESS) can also be performed in specialised centres with appropriately skilled surgeons and specialised equipment with good outcomes [10].

Unfortunately, bilateral adrenalectomy will inevitably commit the patient to lifelong steroid dependence, altered quality of life and the potential for acute adrenal insufficiency [11]. The ideal surgery for bilateral pheochromocytoma will be to remove all of the medulla but retaining the cortex, an impossible task in reality [12]. Current surgical techniques of cortical sparing adrenalectomy aim to preserve a portion of vascularised adrenal cortex to retain corticosteroid production capability, while at the same time achieving an acceptably low recurrence rate of the primary disease. The benefits of cortical sparing adrenalectomy has been well documented in the literature [13]. A multinational observational retrospective population-based study by Castinetti, et. al. in 2014, demonstrated 43% steroid dependency and 3% recurrence after 6-13-years in adrenal-sparing surgery versus 100% steroid dependency and 2% recurrence in total adrenalectomy surgery [14].

In our case report, we present a series of synchronous bilateral retroperitoneoscopic adrenalectomy, two of which are cortical sparing and one total adrenalectomy. They were performed in a tertiary center by a group of specialised endocrine surgeons in Western Australia, Perth. In selected patients undergoing elective bilateral adrenalectomy, we

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prefer to utilise a synchronous approach as it allows for significantly shorter anaesthesia periods. We outline our initial workup, biochemistry levels, surgical approach, post-operative care and outcomes in the following three cases.

Case Series

Case 1

Our first patient is a 13-year-old female who was diagnosed with bilateral pheochromocytoma and successfully underwent a synchronous bilateral retroperitoneoscopic adrenalectomy with cortical sparring on the right side. She first presented with a 12-month history of feeling flushed with ongoing diaphoresis and persistent hypertension. She has no previous medical history. Other than a grandparent with breast cancer, there were no other familial cancer or adrenal pathology.

Initial biochemical analysis revealed raised free nor-metadrenaline of 33400 pmol/L (< 800 pmol/L), free metadrenaline 140 pmol/L (< 400 pmol/L), and 3-Methoxytyramine 490 pmol/L. Chromogranin-A was raised at 307µg/L (< 102 µg/L).

Whole body computed tomography (CT) was performed and bilateral adrenal arterial-enhancing masses were identified. Ultrasound thyroid was performed as part of multiple endocrine neoplasia (MEN) syndrome workup with no thyroid lesion identified. 18F-fluorodeoxyglucose positron emission tomography (PET) was performed, and bilateral adrenal masses were intensely tracer-avid, in keeping with bilateral pheochromocytoma. No definite DOPA-avid nodal metastatic disease or distant metastatic disease was identified.

As part of preoperative medical management, she was commenced on 2 mg phenoxybenzamine three times daily for four weeks prior to her planned surgery. A synchronous bilateral retroperitoneoscopic adrenalectomy with cortical sparring on the right side was performed. Our patient was placed in a modified jack-knife prone position and two separate endocrine teams performing synchronous surgery bilaterally. Entry into right retroperitoneum was gained through Hassan technique placing balloon port just below the tip of 12th rib and two 5mm ports on the right flank. Gerota fascia was entered, and the right kidney identified. The superior pole of right kidney was mobilised. Right kidney vessels were identified and preserved. Right adrenal gland was mobilised inferiorly, laterally, and medially. Right adrenal vein was identified and doubly ligated with Ligasure and divided. The adrenal tumour was excised with small margin of normal adrenal tissue leaving remnant of adrenal cortical tissue. Endocatch was used to remove specimen. A similar approach on the left side took place synchronously. Left adrenal vein was identified, ligated and divided. The adrenal tumour was removed in completeness, including extra tissue at the superior pedicle. Haemostasis achieved with very minimal blood loss. There were no intraoperative complications.

Histology revealed the right adrenal gland tumour to be a pheochromocytoma, moderately differentiated (GAPP score 3), PASS score 4 with no lymph vascular invasion, clear of margins. Left adrenal gland was a pheochromocytoma, 54mm, moderately differentiated (GAPP score 4), PASS score 4, with lymph vascular invasion. Both tumours show loss of staining for SDH-B and retention of staining for SDH-A.

Our patient was admitted to ICU post procedure for close blood pressure monitoring. Phenoxybenzamine was ceased post-operatively and IV hydrocortisone 50 mg, 4-hourly was commenced. Day 2 post-operative serum cortisol was within normal ranges at 120 nmol/L (100-600 nmol/L). Over the next 3 days, IV hydrocortisone was gradually tapered and synacthen stimulation test day 6 post adrenalectomy showed normal adrenal response (cortisol baseline 300 nmol/L, 30min post synacthen 390 nmol/L, 60min post 430 nmol/L). Biochemistry on day 6 post-adrenalectomy revealed normal free nor-metadrenaline level at 440 pmol/L (< 800 pmol/L), free metadrenaline at < 30 pool/L (< 400 pmol/L), and 3-Methoxytyramine at 15 pmol/L.

Our patient had an unremarkable recovery and required no medications on discharge. She was educated on sick day management and given an emergency plan of Hydrocortisone 200mg IM.Genetic testing was consistent with Von Hippel-Lindau (VHL) syndrome. Ongoing surveillance with serum plasma metanephrine and 3-Methoxytyramine, abdominal imaging and audiometry were organised through our tertiary paediatric hospital.

At 6-month mark, our patient had remained asymptomatic and was not steroid dependent with no requirement of any emergency steroids.

Case 2

Our second patient is a 52-year-old female who was also diagnosed with bilateral pheochromocytoma and successfully underwent synchronous bilateral retroperitoneoscopic adrenalectomy with cortical sparring bilaterally.

She initially presented with small bowel obstruction secondary to infective enteritis which resolved with supportive management. CT Abdomen was ordered as part of the initial workup for bowel obstruction and revealed an incidental finding of bilateral adrenal masses. CT Chest revealed bilateral thyroid nodules measuring up to 23 mm with coarse calcification. Ultrasound thyroid further defined the nodules as bilateral solid thyroid nodules and right sided Level 4 lymph node with central calcification. 18F-fluorodeoxyglucose (F-18 FDG) PET-CT scan revealed the bilateral adrenal mass lesions to exhibit mild FDG-avidity. Octreotate PET-CT showed intense octreotate-uptake within both adrenal glands and left thyroid nodule, low grade octreotate-uptake from right thyroid nodule and mild octreotate activity at right level 4 cervical lymph node. Fluorine-18-l-dihydroxyphenylalanine (18F-DOPA) PET scan showed intense DOPA binding to left and right thyroid nodules, appearance suggestive of multifocal medullary thyroid carcinoma. Bilateral adrenal nodules also demonstrated intense DOPA binding suggestive of bilateral pheochromocytoma. Ultrasound fine needle aspiration was then performed on bilateral thyroid nodules and histology confirmed diagnosis of malignant medullary carcinoma.

Biochemistry was performed and initial free normetadrenaline was raised at 3300 pmol/L (< 750 pmol/L) and free metadrenaline raised at 4290 pmol/L (< 300 pmol/L). Post-dexamethasone cortisol was raised at 284 nmol/l (normal suppression serum cortisol (<50 nmol/l). As part of preoperative medical management, phenoxybenzamine 5mg in the morning and 10mg at night was commenced three weeks prior to her planned surgery.

A synchronous bilateral retroperitoneoscopic adrenalectomy with cortical sparring bilaterally was performed.

Our surgical approach was very similar to Case 1, with again very minimal blood loss and no intraoperative complication. Histology revealed the right adrenal gland tumour to be a pheochromocytoma, PASS score; 6. No loss of SDHB. Left adrenal gland was a pheochromocytoma, PASS score; 8. No loss of SDHB.

Our patient was admitted to ICU post procedure for close blood pressure monitoring. Her day 1 post-operative serum cortisol was noted to be low at 57 (150 - 700 nmol/L). Hence, she was commenced on replacement Hydrocortisone 20 mg at 7am, 10 mg at 2pm and fludrocortisone 50microg at 8am. Our patient had an otherwise unremarkable recovery and discharged day 2 post post-adrenalectomy.

Total thyroidectomy with bilateral central and lateral neck dissection was performed 3 months post adrenalectomy which confirmed bilateral medullary thyroid cancer stage pT2pN1bMx, 7/25 lymph nodes confirmed for metastatic tumour. Serum calcitonin peaked at 4400 in her pre-operative period, before falling to 4 ng/L (< 5.1) 4 months post-operation indicating good prognosis. Optimal TSH suppression was achieved with thyroxine 100mcg/50mcg alternate days.

Genetic testing was consistent with a RET gene mutation for multiple endocrine neoplasia type 2. At 6-month mark, her steroid requirements were Hydrocortisone 12mg at 8am, 8mg at 2pm and Fludrocortisone 50 microgram at 8 am. Repeat imaging showed no recurrence in adrenal bed.

Case 3

Our third patient is a 62-year-old female with ACTH dependent cushings syndrome secondary to a functioning pituitary macroadenoma which failed pituitary surgery, radiotherapy, and medical management. Synchronous bilateral retroperitoneoscopic total adrenalectomy was performed to control her hypercortisolism.

Our patient first presented in 2015 with 6-month history of cushingoid features. Her plasma ACTH levels were raised at 60.2 pmol/L (2-10 pmol/L) and serum cortisol post 8mg dexamethasone suppression was 460nmol (150 - 700nmol/L). Inferior petrosal sinus sampling was performed which confirmed centrally secreting ACTH. MRI pituitary revealed a large bi-lobed enhancing soft tissue mass arising from the pituitary fossa and given the ACTH dependent Cushings syndrome, a diagnosis of functioning pituitary macroadenoma was made. Due to bitemporal visual field loss and progressive cushing's syndrome poorly controlled with medical therapy, endoscopic transsphenoidal resection was performed elective in 2015. Histology revealed an atypical adenoma with capacity for aggressive local invasion and recurrence. Close following up imaging identified residual tumor, with mild increase in size five months post-resection

Over the next 5-years, patient underwent multiple rounds of adjuvant radiotherapy. Unfortunately, she continued to exhibit symptoms of worsening cushingoid symptoms such as weight gain and hypertension poorly controlled with prazosin and perindopril. By 2020, despite being on Ketoconazole 200mg TDS for hypercortisolism, her systolic blood pressure remained poorly controlled around 190 to 200mmHg while on Prazosin 2mg BD and Perindopril 10 mg mane. She also reported uncontrollable weight gain of more than 10 kilograms over the past year. Her plasma ACTH remained in the ranges of 50 to 60 pmol/L (2-10 pmol/L) and 24hr free urine cortisol was more then 610 nmol/d (< 330nmol/d)

Given that our patient had ACTH-dependent Cushing's syndrome with aggressive Nelson's syndrome resulting in failure of trans-sphenoidal surgery, minimal improvement after over forty rounds of radiotherapy and maximal medical therapy, a joint decision was made to proceed with bilateral adrenalectomies to manage her hypercortisolism.

A synchronous bilateral retroperitoneoscopic total adrenalectomy was performed. Our surgical approach was very similar to Case 1, with again very minimal blood loss and no intraoperative complication. Histology revealed nodular adrenal hyperplasia, consistent with the history of Cushing's disease.

Our patient was admitted to ICU post procedure for close blood pressure monitoring. Given her severe hypercortisolism pre-operatively, she was commenced on fludrocortisone 100microg mane and hydrocortisone 70mg daily, with a plan for gradual down titration. Our patient had an otherwise unremarkable recovery and discharged day 2 post post-adrenalectomy. She was educated on sick day management and given an emergency plan, with plan for close endocrine follow-up.

At 6-month mark, her steroid regime was with Hydrocortisone 14mg at 8am, 10mg at 2pm, 4mg at 8pm, with Fludrocortisone 10microgram at 8am. Unfortunately, our patient had further progression of her atypical pituitary adenoma and is now participating in clinical trials.

Conclusion

Synchronous bilateral cortical sparing retroperitoneoscopic adrenalectomies are safe to perform with short intraoperative and recovery times, with minimal complications in the intraoperative and recovery period. We had close endocrinology input throughout the pre-and post-operative period for all our patients. We also admitted all patients post-operatively to the intensive care unit for close blood pressure monitoring and steroid replacement or down-titration. We attribute our low complication rates to this protocol.

The benefits of cortical sparing adrenalectomy in selected patient population have been well documented, and

Table 1: Literature Review on PubMed with keywords 'laparoscopic', 'cortical sparing', 'synchronous / simultaneous' and 'bilateral adrenalectomy' from year 1996 to 2020

Primary Author	Indication	Patients that underwent Laparoscopic Cortical-Sparing Simultaneous Bilateral Adrenalectomy	Complications	Steroid independence	Adrenal beds that underwent Cortical-Sparing adrenalectomy	Recurrence of primary disease	Year
Hartmut P. H. Neumann	Bilateral pheochromocytoma	4	8	0	4 of 4 (100%)	0	1999
William B. Inabnet	Bilateral pheochromocytoma	5	10	0	not reported	3 (30%)	2000
Michael Brauckhoff	1)Bilateral pheochromocytoma 2)Bilateral adrenocortical hyperplasia	2	16	0	1 of 2 (50%)	0	2003
Linwah Yip	Bilateral pheochromocytoma	26	30	0	17 of 26 (65%)	3 (10%)	2004
Eric K. Diner	Bilateral pheochromocytoma	10	43	0	not reported	2	2005
Raffaele Pugliese	Bilateral pheochromocytoma	1	2	0	1 of 1 (100%)	0	2008
Y. K. Ku	Bilateral pheochromocytoma	1	2	0	1 of 1 (100%)	0	2010
Pier Francesco Alesina	Bilateral pheochromocytoma	32	89	1x: Bleeding requiring reoperation 1x: Cerebral stroke	30 of 32 (94%)	0	2011
K. V. S. Hari Kumar	Bilateral pheochromocytoma	1	2	0	1 of 1 (100%)	0	2011
Elizabeth G Grubbs	Bilateral pheochromocytoma	39	55	1x: Acute adrenal insufficiency	21 of 27 (78%)	4 (7%)	2013
Fouad Aoun	Bilateral pheochromocytoma	1	2	0	1 of 1 (100%)	o	2014
Benjamin R. Biteman	Bilateral pheochromocytoma	1	2	0	1 of 1 (100%)	0	2016
R Morimoto	Bilateral aldosterone-producing adenoma	1	2	0	1 of 1 (100%)	0	2016
Total		**124**	**263**	**3**	**81% (79 of 97)**	**4.6% (12 of 263)**	

synchronous surgery in our experience has led to significantly shorter anaesthesia periods. However, the limitation lies in having multiple surgeons trained in performing this procedure present for the case.

A literature review on PubMed with keywords 'laparoscopic', 'cortical sparing', 'synchronous / simultaneous', 'bilateral adrenalectomy' from year 1996 to 2020 is presented in Table 1 [12,15-26]. We can see that there are less then 125 reported cases of synchronous bilateral retroperitoneoscopic cortical sparring adrenalectomy in the literature, many of which are single center case series. Given the benefits of a synchronous approach, it is in hope that our contribution will benefit the scientific community, allowing for retrospective cohort studies in the future.

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