Original Article

Bilateral adrenalectomy for Cushing's syndrome: Pros and cons

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ABSTRACT

Aim: To assess the outcome of patients undergoing bilateral adrenalectomy for Cushing's syndrome (CS). **Methods:** All patients who underwent bilateral adrenalectomy for CS at the Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences hospital between 1991 and 2013 were included. Medical records were reviewed to obtain patient characteristics and follow-up data. **Results:** Twenty-seven patients were studied. Mean age was 28.74 ± 12.95 years (range 9–60), male:female ratio was 1.7:1. About half that is, 48.19% were of Cushing's disease (failed trans-sphenoidal surgery [TSS]), 37.04% were of ectopic CS (ECS), and 14.81% were of CS due to bilateral adrenal pathology. Median follow-up period was 80.5 months. Before surgery, 74.1% patients had body mass index >25 which after surgery declined to <25 in 75% of them. Hypertension was present in 85.2% and after surgery resolved in 40%. Diabetes mellitus was present in 44.4% and after surgery resolved in 33% of them. Hirsutism and proximal muscle weakness were present in 55.6% and 70.4% patients, respectively, and after surgery improved markedly in all patients. Adrenal crisis developed in 36.3% and Nelson's syndrome in 41.7% patients during follow-up. Three patients died in perioperative period while three succumbed to the disease during follow-up. Two patients developed recurrence of endogenous cortisol production during the follow-up period. **Conclusions:** Bilateral adrenalectomy is a valid treatment option for palliating severe symptoms in Pituitary Cushing's with failed TSS and unlocalized ECS but the procedure is curative for CS due to bilateral adrenal disease. Overall morbidity and mortality is higher than other endocrine operations. Co-morbidities tend to be more severe and are a risk factor for mortality during the time patient survives.

Key words: Bilateral adrenalectomy, Cushing's syndrome, morbidity, mortality, survival

Introduction

From the time of Harvey Williams Cushing in 1912, when the first case was reported till this era, patients with subtle symptoms of Cushing's syndrome (CS) are difficult to diagnose and manage. The morbidity and mortality have decreased significantly over the years but still the diagnosis remains difficult and consequently many cases are missed in the early stages. Although clinical manifestations include centripetal obesity, hypertension, impaired glucose tolerance, menstrual and sexual dysfunction, hirsutism, acne, striae, emotional liability, and osteoporosis but the most discriminating features are broad violaceous striae on atypical locations, children with short stature and weight gain, easy bruising, proximal muscle weakness, facial plethora which may be difficult to detect in dark skinned person.[1,2]

Although steroid abuse in the society remains the most common cause of CS, pituitary dependent Cushing's

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disease (CD) is the most common cause of endogenous CS. Most (90%) of the cases of endogenous CS are adrenocorticotropic hormone (ACTH) dependent either from the pituitary (80%) or from some ectopic sources (10%). Approximately, 10% of cases are ACTH independent, caused by some adrenal lesions (adenoma/carcinoma) and rarely primary bilateral adrenal hyperplasia.[3] Trans-sphenoidal resection of pituitary tumor is the first line of treatment option for the patients of CD. Despite advances in pituitary surgery, remission occurs in only 70–85% cases and unfortunately it fails in 10–30% cases.[4] Presumably due to small microadenoma not being detected on magnetic resonance imaging (MRI) and inferior petrosal sinus sampling (IPSS) needs expertise. Hence, even in the modern era, there is a role of bilateral adrenalectomy for palliating the severe symptoms.

In ectopic CS (ECS), the physician refers the patient to the surgeon after searching for the ectopic which is not localized or the patient is too sick to wait till an ectopic is localized. After an informed decision with involvement of patient, his relatives, and his treating physician, the surgeon may have to resort to bilateral adrenalectomy. In patients of CS with bilateral adrenal pathology, bilateral adrenalectomy is the obvious treatment option.

The purpose of this retrospective study was to assess the outcome of patients of bilateral adrenalectomy for CS as very less data on the outcome of bilateral adrenalectomy in an Indian population, is available in the literature.

Methods

During the study period spanning 23 years (1991–2013), of the 406 patients undergoing adrenalectomy at the Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, only 47 (11.58%) patients underwent bilateral adrenalectomy. Of these 47 patients, only 27 patients underwent bilateral adrenalectomy for CS. Medical records were analyzed to obtain patient demographics, operative findings, pathology, and follow-up details. Etiology of CS included patients of ACTH secreting pituitary adenoma with failed trans-sphenoidal surgery (TSS), unlocalized source of ectopic ACTH production and primary adrenal hyperplasia. The diagnosis was arrived at on the basis of clinical details, biochemical analysis, radiological investigations, and others as per the algorithm[5] depicted as Figure 1.

After preoperative preparation, all patients underwent bilateral adrenalectomy under steroid cover either by open or laparoscopic route. In our institution, laparoscopic adrenalectomy (although unilateral) for patients of CS was started in 1998 and first laparoscopic bilateral adrenalectomy for CS (for unlocalized ECS and CS after failed TSS) was performed in 2003. At the time of discharge, patients, and their families were counseled about regular steroid intake and strict follow-up. Patients were also issued a standard card indicating the operative procedure and instructions for regular intake of steroids. After discharge from the hospital, patients were called for periodical checkup and review.

Follow-up data were collected from hospital records, letters, email, and telephonic contacts. Two patients were lost to follow-up while 3 patients died in the perioperative period. Thus, follow-up data were available for only 22 patients. Statistical analysis was done using SPSS for windows - version 17.0 software. Data were analyzed by nonparametric tests using Wilcoxon signed rank test and two sample *t*-test while survival was analyzed by Kaplan–Meier test. Follow-up and survival figures were expressed in months. Data were expressed as a mean ± standard deviation.

Results

Of the total 27 patients having undergone bilateral adrenalectomy 13 (48.19%) belonged to pituitary CD with failed pituitary surgery, 10 (37.04%) were diagnosed as ECS and 4 (14.81%) were diagnosed to have CS due to bilateral primary adrenal hyperplasia [Table 1]. Patients characteristics were listed in Table 2. The mean age was 28.74 ± 12.95 (9–60) years, with a male: female ratio of 1.7:1. The mean serum cortisol level prior to surgery was 1065.97 ± 564.12 nmol/L (range 510–2540), with a huge difference between patients with ECS (1217.36 ± 648.63 nmol/L, range 510–2540)

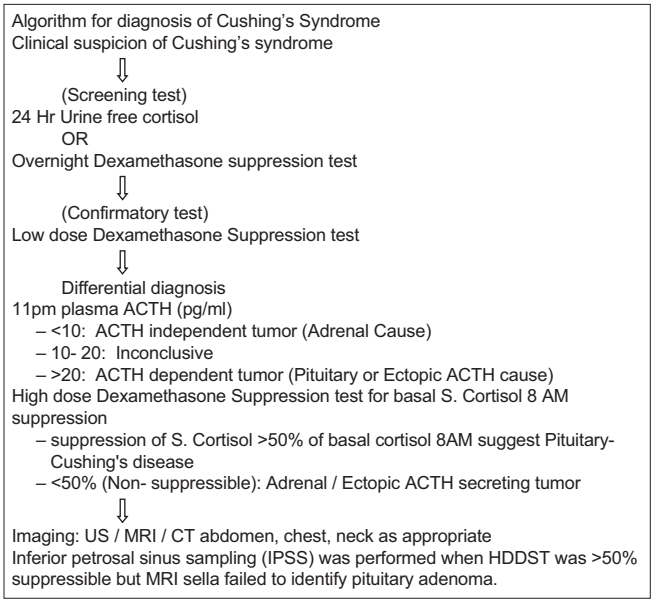

Figure 1: Algorithm for diagnosis of Cushing's Syndrome

Table 1: Etiology of Cushing's syndrome

Etiology	Number of patients (%)
ACTH dependent	
Pituitary source (failed TSS)	13 (48.19)
Ectopic ACTH source	10 (37.04)
ACTH independent	
Primary pigmented nodular adrenal hyperplasia	3 (11.11)
Bilateral macronodular hyperplasia	1 (3.70)

ACTH: Adrenocorticotropic hormone; TSS: Trans-sphenoidal surgery

Table 2: Patient characteristics

Total patients	27
Male/female	17/10
Age at the time of surgery (mean+SD)	28.74±12.95 years
BMI prior to surgery (mean+SD)	27.39±3.99 kg/m^2
Serum cortisol prior to surgery (mean+SD)	1087.79±567.37 nmol/L
Serum ACTH prior to surgery (mean+SD)	120.66±117.14 pg/ml

ACTH: Adrenocorticotropic hormone; SD: Standard deviation

and those with adrenal CS (759.67 ± 81.47 nmol/L, range 684–845.90 nmol/day), while the cortisol values for pituitary CD was in between (1041.62 ± 569.75 nmol/L, range 522.99–2358). The mean serum ACTH prior to surgery was 115.69 ± 112.34 (range 59.43–449) for patients with CD while it was 93.60 ± 85.14 (range 15.36–238) for patients with ECS. In 11 patients despite ACTH being high, MRI failed to localize any pituitary tumor. Consequently, these patients underwent IPSS (IPSS to localize central or peripheral source of ACTH). The IPSS assigned the ACTH source to central location (pituitary) in 5 patients and peripheral location in 6 patients. In 5 patients, in which IPSS assigned the ACTH source to central location, pituitary surgery was done but it failed twice.

All patients underwent bilateral adrenalectomy either by open or laparoscopic technique. Laparoscopic adrenalectomy was tried in 12 patients but had to be converted to open technique in 8 patients, whereas could be successfully performed in 4 patients. The median adrenal gland weight on the right side was 18 g (range: 1.7–180 g) and on the left side was 14 g (range: 2–160 g). Irrespective of the surgical approach, the procedure was safely executed without any significant intra-operative complications. Postoperative complications occurred in 3 patients (11%), include pneumonia in 1 patient, lower lobe atelectasis of the right lung in 1 patient and fecal fistula in 1 patient. All these complications were successfully managed and the patients discharged from the hospital. Histopathology of bilateral adrenalectomies in CS (due to primary adrenal hyperplasia) was primary pigmented nodular adrenal hyperplasia (PPNAD) in 3 patients and macronodular hyperplasia in 1 patient. Histopathology of the resected adrenals in all patients of CD and ECS was reported as hyperplasia of the adrenal gland.

Median follow-up period was 80.5 months (range 2-157 months). Two patients were lost to follow-up despite repeated attempts to contact them. Prior to surgery 51.9% (n = 14) patients were overweight (body mass index [BMI] >25) and 22.2% (n = 6) patients were frankly obese (BMI >30). A large majority (75%) of the total patients who were overweight and obese (BMI >25), lost excess weight and attained BMI <25 after surgery, the difference being statistically significant (P < 0.001). Statistically significant improvement was seen in hypertension (85% [n = 23] to 40%) (P < 0.005), in 50% patients requirement of anti-hypertensive was reduced while 10% patients remained hypertensive. Similarly, significant improvement was observed among diabetics. Prior to surgery 44.4% (n = 12) were diabetic and only 11% (n = 3/27) remained diabetic after surgery (P < 0.05). Of 75% (9/12) of diabetics which showed improvement after surgery, in 4 patients blood sugar was within normal limit without any anti-diabetic medication and in 5 patients sugar was better controlled with lower doses of oral hypoglycemic agents/insulin. Hirsutism was present in 55.6% (n = 15) patients before surgery and resolved in all patients after surgery. Proximal muscle weakness was present in 70.4% (n = 19) patients but normalized in all patients.

Acute adrenal insufficiency occurred in 36.3% patients (n = 8/22). Of these, single episode of acute adrenal insufficiency occurred in 22.7% patients (n = 5/22), whereas 13.6% patients (n = 3/22) experienced 2 or more such episodes. The majority (63.7%) of patients never experienced any adrenal crisis. The number of adrenal crises per 100 patient-years was calculated as 10.16. Among CD patients, 41.7% patients (n = 5/12) developed Nelson's syndrome (NS) after a median follow-up of 32 months (range 20–60 months) after bilateral adrenalectomy. Of 5 NS patients, 2 patients underwent repeat TSS, whereas 3 patients underwent irradiation to pituitary fossa.

Two patients developed recurrence of endogenous cortisol overproduction. The first after 6 years and the other after 10 years of surgery. First patient was suffering from primary pigmented nodular adrenal hyperplasia (PPNAD) while the second patient had unlocalized ACTH secreting tumor (ECS).

Overall mortality was 22.2% (n = 6) [Table 3]. Three patients (11.1%) died in the perioperative period while 3 patients succumbed 2, 9, and 36 months after surgery. Mortality figures during the follow-up period were 13.6% (3/22). Analyzing further, 5 deaths (83.2%) occurred within the first year of surgery, whereas 1 patient died after

Table 3: Analysis of mortality during peri-operative and follow up periods

Disease	Age (years)/ sex	Mortality (Periop/follow up)	Post-op. survival	Cause of death
CD	26/male	Periop (on ventilator)	0.5 months	Intracerebral hemorrhage, sepsis, Acute respiratory distress syndrome
ECS	24/male	Periop (on ventilator)	0.5 months	Chest infection, acute respiratory distress syndrome, sepsis
Adrenal CS	60/male	Periop (on ventilator)	3 months	Chest infection, sepsis, multi-organ failure
ECS	37/male	Follow up	2 months	Flare up of preexisting pulmonary tuberculosis, uncontrolled chest infection
Adrenal CS	9/male	Follow up	9 months	Addisonian crisis after diarrhea
ECS	30/female	Follow up	36 months	Addisonian crisis, hypotension

Periop: Perioperative; CS: Cushing's syndrome; CD: Cushing's disease; ECS: Ectopic Cushing's syndrome

3 years postoperatively. Of the 27 patients, a vast majority 78% survived the procedure and reported healthy at the last follow-up. Mean survival following bilateral adrenalectomy was 119.75 ± 13.24 months. Kaplan–Meier curve for survival is shown in Figure 2.

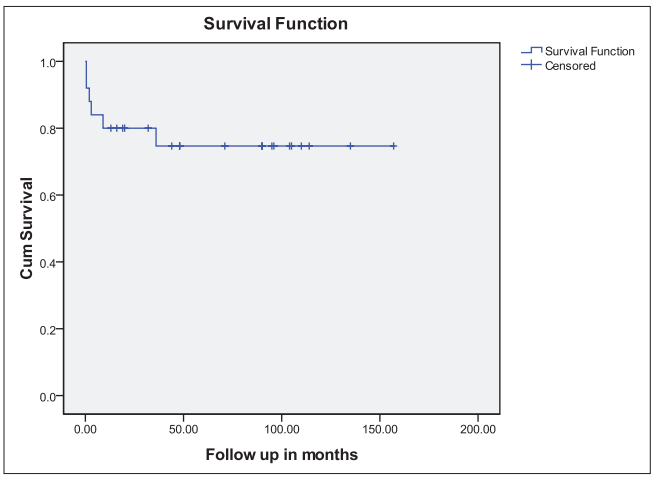

Figure 2: Survival following bilateral adrenalectomy

Discussion

Bilateral adrenalectomy for CS is not as dreaded as it was thought during the olden days. Our data suggests that a large majority of patients will survive the procedure and can be expected to lead a healthy life.

Like other series, in our series too, the majority (48.13%) of patients were CD with failed TSS. In patients of CD, Trans-sphenoidal pituitary surgery remains the mainstay of treatment. Remission after TSS occurs in up to 70–85% patients.[3] In CD patients with failed TSS, four treatment options are available (1) Repeat TSS, (2) Radiotherapy to pituitary fossa, (3) Medical therapy with ketoconazole and pasireotide, and (4) Bilateral adrenalectomy. Although immediate repeat pituitary surgery is recommended in these patients, however, if repeat surgery also fails, other treatment options are advised.[4,6] In our series, we encountered 37.04% of ECS patients (which included patients with unlocalized ACTH producing tumor) in which IPSS suggested the peripheral source of ACTH production. Yet no tumor could be localized on peripheral imaging. However, during the follow-up period tumor could be localized in two patients. One patient had an ACTH producing tumor localized to the apical segment of the lower lobe of right lung while in other patient it was localized to the thymus gland. Resection of the tumor at both these sites resulted in normalization of ACTH levels in both the patients, postoperatively till the latest follow-up visit.

Our patients were younger at the time of diagnosis and surgery (mean age at time of surgery 28.74 years) as compared to patients in other series[7-9] where they were older and male patients were more in our study (63%), whereas in other series females more.[7-9]

Although in our series, we had fewer cases operated laparoscopically but the procedure has become the standard of care now. Bilateral retroperitoneoscopic adrenalectomy via the posterior approach has become more popular among surgeons due its inherent advantages and avoiding the change in position of the patient at the table. Laparoscopic surgery for adrenal gland was started in 1998 in our institution and has become increasingly popular.

Postoperative complications in our series include basal atelectasis, pneumonia, and drain site infections. One patient develop fecal fistula in the postoperative period that was managed successfully by conservative means.

Most of the patients in our series were overweight (mean BMI = 27.39 ± 3.99 kg/m^2), whereas most of the patients in other series were obese with mean BMI >30 kg/m^2 (mean BMI - 35.7[10] and 35.0[9]). Clinical improvement was seen in most of the patients after bilateral adrenalectomy. Around 75% of our patients showed improvement in obesity and diabetic status and more than 90% patients showed improvement in blood pressure control, proximal myopathy, hirsutism, and psychiatric symptoms. Some symptoms of CS persist despite achieving biochemical normal cortisol levels after surgery. Although there is an improvement in symptoms and quality of life after bilateral adrenalectomy, yet

it remains a little inferior when compared with the matched population.[9,11] Psychiatric disorders and chronic fatigue persist long after achieving biochemical normocortisolism.[8,12] The quality of life after bilateral adrenalectomy does not appear to be different in patients treated with laparoscopic when compared with an open approach.[11]

The adrenal crisis remains a dreaded sequelae of bilateral adrenalectomy and persists as an important cause of morbidity and sometimes mortality in these patients. In our series, 36.3% patients develop at least one episode of adrenal crisis during a median follow-up of 80.5 months, whereas it varied between 9% and 64% with a median rate of 28% in other series[13] [Table 4]. In a study almost 25% of patients treated by bilateral adrenalectomy had at least one episode of adrenal crisis requiring admission to the hospital and administration of intravenous saline with corticosteroids.[14] In a recently published review on the outcome of bilateral adrenalectomy, the incidence of the adrenal crisis was 9.3/100 patient-year, whereas it was somewhat higher in our patients (10.16/100 patient-year).[13] Patients experiencing the first attack are much more prone to die than those who have already experienced it but survived. Sadly 2 out of 5 of our patients who experienced the first attack of crisis died on the way to the hospital. However, all the 3 patients who experienced multiple attacks of adrenal crisis did survive. An adrenal crisis leading to mortality after bilateral adrenalectomy remains the most fearsome squeal among the minds of surgeons. As our data shows, a majority of patients do survive and can be expected to lead a near normal life. By adequate glucocorticoid substitution and education of patients after bilateral adrenalectomy, adrenal crisis can be managed and prevented.

In our series, we found 41% of our patients develop NS and the incidence varies widely between 0% and 47%[13] [Table 4]. The diagnostic criteria of NS remain controversial, and a firm consensus is still lacking.

Table 4: Comparison of outcome with other series

Author	NS (%)	Adrenal crisis (%)	Mortality in follow up (%)	Follow up (months)
Thompson SK. *et.al.*[9]	8.3	N/A	3	42
Smith PW.*et.al.*[10]	18	N/A	5	60
Gil- Cardenas A. *et.al.*[18]	28	N/A	6	41
Tiyadatah BN. *et.al.*[23]	38	N/A	16	33
Assie G. *et.al.*[16]	40	N/A	4	55
Chow JT. *et.al.*[8]	N/A	N/A	10	N/A
Our series	41	36	13	80

NS: Nelson's syndrome

Following bilateral adrenalectomy,[15,16] the diagnosis of NS is based on:

- Growing residual pituitary adenoma
- ACTH levels >300 mg/dl
- Hyperpigmentation of the skin.

In 2010 in a review study on NS, Barber *et al*.,[17] laid down a new diagnostic criteria which is, "a patient of bilateral adrenalectomy for CD having at least one of the following two criteria:

- An expanding pituitary tumor in MRI brain
- An elevated level of ACTH to >500 ng/L from a single plasma sample collected at 8.00 AM prior to steroid administration or a rise of ACTH to >30% on at least two consecutive occasions."

A study demonstrated that NS is a frequent complication after bilateral adrenalectomy and developed in 28% of patients.[18] Several factors that can predict development of NS are high basal level of ACTH after adrenalectomy, young age at adrenalectomy, presence of pituitary tumor before adrenalectomy, prophylactic pituitary radiotherapy, subnormal steroid replacement, pre-treatment urinary cortisol level, and female gender. Of these, the high basal level of ACTH after adrenalectomy remains the best predictive factor.[11,19-21] Prophylactic pituitary radiotherapy is a protective factor against the development of NS.[11,22]

Surprisingly in 2 of our ECS patients, source remained unidentified initially but could be detected only during the follow-up. Once identified, these patients underwent surgery and the tumor was excised successfully. Based on these observations is it wise not to rush for bilateral adrenalectomy in these patients. Repeated imaging studies over a period of time may unveil the primary source, which then may become amenable to surgery at a later date. However, this approach remains controversial as a delay in surgery can lead to worsening of CS, and, therefore, poor quality of life. If survival is a problem and primary/ectopic is not identified, then bilateral adrenalectomy is to be strongly considered.

Overall mortality

Overall mortality in our series was 22% which is quite well-comparable to mortality in other series and varies from 0% to 88% (median 17%) at a median follow-up of 41 months[13] [Table 4]. Three patients died in the perioperative period including one patient at 3 months after surgery but during the same admission. All the 3 patients presented with severe muscle weakness preoperatively and despite successful and uneventful surgery could not

be weaned off postoperatively from the ventilator due to the poor respiratory effort. They developed repeated chest infections and despite best ICU care succumbed to sepsis and multi-organ failure.

Mortality during follow-up

Overall, 13.6% patient died during the follow-up period. The mortality was the highest in patient of ECS due to the progression of their underlying disease process after bilateral adrenalectomy.[13] In our study also, the highest mortality (50%) was seen in the patients diagnosed to have ECS. Risk factors for mortality included:

- Male sex (5 males, 1 female)
- Diagnosis of ECS where the source remains undetected
- Prolonged ventilator dependence during the postoperative period.

Most of the deaths occurred in perioperative and in the early follow-up period. Causes include recurrent chest infections, hypercortisolism and immunosuppression causing increased susceptibility to infection, muscle weakness, and poor respiratory effort leading to recurrent lower respiratory tract infections. Mortality during long-term follow-up could be attributed to adrenal crisis.

Conclusions

Bilateral adrenalectomy is a valid treatment option for the management of manifestations of hypercortisolism in patients of CS. It provides good palliation in CD with failed TSS and unlocalized ECS while the procedure is curative for bilateral adrenal CS patients. The majority of patients experience good survival and a good quality of life. However, a higher morbidity and mortality do occur if co-morbidities are more severe during the preoperative period. Despite advances in medical sciences, the procedure carries higher morbidity and mortality but may still need to be done in some patients where other treatment options fail. Due to inherent complexities involved in diagnosis, management, postoperative care, and follow-up, the procedure should be performed only in well-equipped and experienced centers.

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Conflicts of interest

There are no conflicts of interest.

References

1. Nieman L, Cutler GB Jr. Cushing's syndrome. In: Degroot LJ, Besser M, Burger HG. Editors. Endocrinology. 3rd ed. Philadelphia, PA: WB Saunders; 1995. p. 1741-69.
2. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, *et al*. The diagnosis of Cushing's syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008;93:1526-40.
3. Tanagho EA, McAninch JW. Smith's General Urology. 16th ed. New York: Lange; 2004. p. 492-3.
4. Locatelli M, Vance ML, Laws ER. Clinical review: The strategy of immediate reoperation for transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 2005;90:5478-82.
5. Mishra AK, Agarwal A, Gupta S, Agarwal G, Verma AK, Mishra SK. Outcome of adrenalectomy for Cushing's syndrome: Experience from a tertiary care center. World J Surg 2007;31:1425-32.
6. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, *et al*. Transsphenoidal resection in Cushing's disease: Undetectable serum cortisol as the definition of successful treatment. Clin Endocrinol (Oxf) 1993;38:73-8.
7. Alberda WJ, van Eijck CH, Feelders RA, Kazemier G, de Herder WW, Burger JW. Endoscopic bilateral adrenalectomy in patients with ectopic Cushing's syndrome. Surg Endosc 2012;26:1140-5.
8. Chow JT, Thompson GB, Grant CS, Farley DR, Richards ML, Young WF Jr. Bilateral laparoscopic adrenalectomy for corticotrophin-dependent Cushing's syndrome: A review of the Mayo Clinic experience. Clin Endocrinol (Oxf) 2008;68:513-9.
9. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC. Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: A 10-year experience. Ann Surg 2007;245:790-4.
10. Smith PW, Turza KC, Carter CO, Vance ML, Laws ER, Hanks JB. Bilateral adrenalectomy for refractory Cushing disease: A safe and definitive therapy. J Am Coll Surg 2009;208:1059-64.
11. Hawn MT, Cook D, Deveney C, Sheppard BC. Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease. Surgery 2002;132:1064-8.
12. O'Riordain DS, Farley DR, Young WF Jr, Grant CS, van Heerden JA. Long-term outcome of bilateral adrenalectomy in patients with Cushing's syndrome. Surgery 1994;116:1088-93.
13. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, *et al*. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: A systematic review. J Clin Endocrinol Metab 2013;98:3939-48.
14. Lairmore TC, Ball DW, Baylin SB, Wells SA Jr. Management of pheochromocytomas in patients with multiple endocrine Neoplasia type 2 syndromes. Ann Surg 1993;217:595-601.
15. Van Aken MO, Pereira AM, Van Den Berg G, Romijn JA, Veldhuis JD, Roelfsema F. Profound amplification of secretory-burst mass and anomalous regularity of ACTH secretory process in patients with nelson's syndrome compared with Cushing's disease. Clin Endocrinol (Oxf) 2004;60:765-72.
16. Assié G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X. The Nelson's syndrome revisited. Pituitary 2004;7:209-15.
17. Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N, Wass JA. Nelson's syndrome. Eur J Endocrinol 2010;163:495-507.
18. Gil-Cárdenas A, Herrera MF, Díaz-Polanco A, Rios JM, Pantoja JP. Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. Surgery 2007;141:147-51.
19. Pereira MA, Halpern A, Salgado LR, Mendonça BB, Nery M, Liberman B, *et al*. A study of patients with Nelson's syndrome. Clin Endocrinol (Oxf) 1998;49:533-9.

20. Imai T, Funahashi H, Tanaka Y, Tobinaga J, Wada M, Morita-Matsuyama T, *et al.* Adrenalectomy for treatment of Cushing syndrome: Results in 122 patients and long-term follow-up studies. World J Surg 1996;20:781-6.
21. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 1996;81:2647-52.
22. Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ. Neurosurgical treatment of Nelson's syndrome. J Clin Endocrinol Metab 2002;87:5465-9.
23. Tiyadatah BN, Kalavampara SV, Sukumar S, Mathew G, Pooleri GK, Prasanna AT, *et al.* Bilateral simultaneous laparoscopic adrenalectomy in Cushing's syndrome: Safe, effective, and curative. J Endourol 2012;26:157-63.