

Long-Term Outcome of Primary Bilateral Macronodular Adrenocortical Hyperplasia After Unilateral Adrenalectomy

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Context: Unilateral adrenalectomy has been proposed in selected patients with primary bilateral macronodular adrenocortical hyperplasia (PBMAH), but its long-term outcome is unclear.

Objective: The aim of this study was to analyze long-term clinical and biochemical outcomes of unilateral adrenalectomy vs bilateral adrenalectomy in patients with PBMAH in comparison with the outcome of cortisol-producing adenoma (CPA) treated with unilateral adrenalectomy.

Design: Retrospective observational study in three German and one Italian academic tertiary care center.

Patients and Methods: Twenty-five patients with PBMAH after unilateral adrenalectomy (unilat-ADX-PBMAH), nine patients with PBMAH and bilateral adrenalectomy (bilat-ADX-PBMAH), and 39 patients with CPA and unilateral adrenalectomy (unilat-ADX-CPA) were included.

Results: Baseline clinical and biochemical parameters were comparable in patients with unilat-ADX-PBMAH, bilat-ADX-PBMAH, and unilat-ADX-CPA. Directly after surgery, 84% of the patients with unilat-ADX-PBMAH experienced initial remission of Cushing syndrome (CS). In contrast, at last follow-up (median, 50 months), 32% of the patients with unilat-ADX-PBMAH were biochemically controlled compared with nearly all patients in the other two groups ($P = 0.000$). Adrenalectomy of the contralateral side had to be performed in 12% of the initial patients with unilat-ADX-PBMAH. Three of 20 patients with unilat-ADX-PBMAH (15%) died during follow-up, presumably of CS-related causes; no deaths occurred in the other two groups ($P = 0.008$). Deaths occurred exclusively in patients who were not biochemically controlled after unilateral ADX.

Conclusions: Our data suggest that unilateral adrenalectomy of patients with PBMAH leads to clinical remission and a lower incidence of adrenal crisis but in less sufficient biochemical control of hypercortisolism, potentially leading to higher mortality. (*J Clin Endocrinol Metab* 104: 2985–2993, 2019)

Endogenous Cushing syndrome (CS) is a severe disease characterized by excessive glucocorticoid production (1). In ~20% of cases, cortisol is secreted autonomously by the adrenal cortex (2). Adrenal CS is mostly caused by unilateral cortisol-producing adrenal adenomas (CPAs) and less frequently by cortisol-secreting carcinomas. Very rare causes are primary bilateral macronodular adrenocortical hyperplasia (PBMAH), bilateral CPAs, and primary pigmented micronodular adrenal disease (3, 4).

PBMAH presents on imaging with characteristic multiple bilateral macronodules (>10 mm) with hyperplasia and/or internodular atrophy (5). Pathophysiologically, the expression of aberrant membrane receptors in the adrenal cortex plays an important role (4). In most instances, PBMAH is a sporadic disorder, although familial cases have been described (6). Biallelic inactivating variants in the tumor suppressor gene *Armadillo* repeat containing 5 (*ARMC5*) is a frequent cause of PBMAH (7). Characteristically, a germline and a somatic tissue-specific gene variant are required for the development of PBMAH, which is consistent with the two-hit hypothesis of tumorigenesis (8).

Treatment of choice to control hypercortisolism in patients with PBMAH is bilateral adrenalectomy, which inevitably results in lifelong glucocorticoid dependence and, thereby, a risk of adrenal crisis (6). To avoid the induction of adrenal insufficiency, resection of only one adrenal gland has been advocated. Indeed, several recent studies have reported clinical and biochemical improvement after unilateral adrenalectomy (9–13). However, the number of documented patients and associated follow-up time is limited. Here, we report the largest series of patients with PBMAH after unilateral adrenalectomy with analysis of long-term results regarding biochemical and clinical outcomes as well as morbidity and mortality. We compare their outcome with patients with PBMAH treated with bilateral adrenalectomy and with patients with CPA treated with unilateral adrenalectomy.

Subjects and Methods

Patient cohorts

Patients with adrenal CS were recruited from four European academic tertiary centers [Medizinische Klinik IV, Munich (n = 52); Endocrinology in Charlottenburg, Berlin (n = 15); S. Orsola-Malpighi Hospital, Bologna (n = 10); and Division of Endocrinology and Diabetes, Department of Internal Medicine I, University Hospital Würzburg (n = 8)]. German patients were asked to participate in a long-term evaluation within the German Cushing's Registry CUSTODES (14).

Diagnosis was confirmed by chart review with special focus on histology and radiology. All adrenal scans were

reviewed by a multidisciplinary tumor board, or the original scan was rereviewed by a radiologist. An original scan was not available in five patients with CPA, but all five patients had the typical histology and long-lasting postoperative adrenal insufficiency of at least 19 months, in line with a unilateral CPA. PBMAH was histopathologically defined by the presence of macronodular hyperplasia, whereas unilateral CPAs were specified by single adenomas with atrophic surrounding adrenal tissue. The decision for unilateral adrenalectomy (ADX) in PBMAH was based on several factors that were in most instances analyzed and discussed in a multidisciplinary endocrine patient board: besides imaging characteristics (single adenoma, multiple nodules, atrophic or hypertrophic adrenal cortex) and size differences of the adrenal glands, these decisions were based on cortisol gradients during adrenal vein sampling (15) and uptake in iodine-131 or iodine-123 iodometomidate scintigraphy (16).

Of the 85 patients, 40 were diagnosed with PBMAH, and 45 had unilateral CPAs. Patients who remained without surgery based on personal choice (two with PBMAH, two with CPA) or who had adrenal-sparing subtotal adrenalectomies (four with PBMAH, four with CPA) were excluded from further analysis. The remaining patients were divided according to surgical procedure in PBMAH with unilateral adrenalectomy (unilat-ADX-PBMAH, n = 25), bilateral adrenalectomy (bilat-ADX-PBMAH, n = 9), or CPA with unilateral adrenalectomy (unilat-ADX-CPA, n = 39).

Clinical studies

Epidemiologic, clinical, and biochemical data were extracted from patients' files and entered into an electronic database. Information on medical history and socio-demographic characteristics was obtained by trained and certified staff members during a standardized patient interview. The participants underwent at least one standardized postsurgical medical examination. As part of CUSTODES, the examinations were repeated annually. If not mentioned otherwise, results of the last follow-up are reported. The examination included blood sampling, evaluation of waist-to-hip ratio, and quantification of muscle strength and blood pressure. The latter was measured three times on both arms in a seated position after 5 minutes of rest. The mean of three measurements was used for statistical analysis. Grip strength was assessed with the Jamar hydraulic hand dynamometer (Sammons Preston Rolyan). Mean values of three trials of the leading hand were calculated and compared with median values of an age- and sex-matched normative population (17). For the chair-rising test, the time for rising from a chair (height, 45 cm) five times at maximum speed was taken. The

patient started while seated and ended while standing. Blood samples were taken in the morning from seated subjects who had been fasting.

The study was approved by the local ethical committees (Ethikkommission bei der Medizinischen Fakultät der LMU München, Ethikkommission bei der Medizinischen Fakultät der Universität Würzburg, Ethikkommission der Ärztekammer Berlin and ethics committee of the S. Orsola-Malpighi Hospital of Bologna), and all patients provided written informed consent.

Biochemical measurements

We measured 24-hour urinary free cortisol (UFC) with the Liaison Assay (DiaSorin) or with RIA (Immunotech-Assay, Beckman-Coulter). ACTH and serum cortisol were measured with the Liaison Assay (DiaSorin) or with Immulite (Siemens Healthineers). All other biochemical variables were assayed in the central laboratories of the participating centers using standardized analytical methods.

Definitions

Subjects with blood pressure $\geq 140/90$ mm Hg, self-reported history of hypertension, or intake of antihypertensive medication were classified as hypertensive. Diabetes was defined by HbA1c levels $\geq 6.5\%$ or treatment with antidiabetic drugs. Osteoporosis was defined by T-values -2.5 SD or less using dual-energy X-ray absorptiometry. Cushing stigmata included a large variety of symptoms regarded as disease specific (*e.g.*, moon face, buffalo hump, hirsutism, or skin alterations). Muscle weakness was defined by the self-reported disability to rise from knee bending without the aid of arms. Psychiatric morbidities included self-reported anxiety, depression, panic attacks, or psychosis. Clinical remission of CS was defined by the disappearance of Cushing stigmata. Biochemical remission from CS was defined by dependence on glucocorticoid substitution and/or normalization of dexamethasone-suppressed serum cortisol (<1.8 $\mu\text{g/dL}$) and/or normal UFC excretion (<150 $\mu\text{g}/24$ h).

Genetic testing

Genetic testing was performed as previously described (18). The *ARMC5* coding sequence as well as flanking intronic sequences were amplified by PCR from leukocyte DNA of 11 patients. Both strands of the amplified products were directly sequenced with forward and reverse primers. All mutations were confirmed twice in two independent experiments. The *in silico* software Polyphen-2 (<http://genetics.bwh.harvard.edu/pph2/>) and SIFT version 2 (http://sift.jcvi.org/www/SIFT_enst_submit.html) were used to predict the pathogenic potential of the missense variants. The software Mutalyzer

(Version 2.0.3; <https://mutalyzer.nl/name-checker/>) was used to check the sequence variant nomenclature according to Human Genome Variation Society version 2.0.

Quality of life questionnaires

A generic health-related quality of life (QoL) questionnaire (SF-36 Health Survey) (19) and two disease-specific instruments [Tuebingen CD-25 (20) and Cushing QoL (21)] were used to assess QoL. In each of these questionnaires, values can range from 0 to 100. Higher scores in the SF-36 Health Survey as well as the Cushing QoL and lower scores in the Tuebingen CD-25 indicate better QoL.

Statistical analysis

Data were extracted from the German Cushing's Registry CUSTODES. If not stated otherwise, results are expressed as median and interquartile range (IQR). Data between groups were compared using χ^2 test (two-sided), Mann-Whitney *U* test, or Kruskal-Wallis test. Survival was analyzed using Kaplan-Meier curves. Concerning health-related QoL, Mann-Whitney *U* test was used for comparison of scores between different patient groups. A *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS ver. 25 (IBM).

Results

Surgical procedures in patient groups

Clinical and biochemical parameters at initial diagnosis of CS were comparable between patients with unilat-ADX-PBMAH, patients with bilat-ADX-PBMAH, and patients with unilat-ADX-CPA except for age at diagnosis (Table 1). Two of 10 tested patients with PBMAH were found to carry *ARMC5* mutations.

Initial clinical and biochemical outcome after first surgery

Unilateral adrenalectomy resulted in clinical and biochemical remission in 21 of the 25 (84%) patients with PBMAH. As expected, 100% of the patients with bilat-ADX-PBMAH and unilat-ADX-CPA experienced clinical and biochemical remission (Table 2).

Persistence and recurrence of CS

Adrenalectomy of the contralateral side had to be performed in three (12%) of the patients with PBMAH initially subjected to unilateral adrenalectomy because of persistent or recurrent hypercortisolism. One patient of the bilat-ADX-PBMAH group developed a (clinically silent) para-aortic tumor 20 years after bilateral ADX. This lesion was incidentally detected during CT imaging

Table 1. Clinical and Biochemical Parameters at Diagnosis of CS According to the Underlying Pathology and Surgical Treatment

	Unilat-ADX-PBMAH (n = 25)	Bilat-ADX-PBMAH (n = 9)	Unilat-ADX-CPA (n = 41)	P
Female/male	16/9	5/4	35/4	
Age at diagnosis, y	56 (22), 25	53 (35), 9	45 (19), 39	0.026
Time from first symptoms to diagnosis, mo	22 (27), 15	39 (69), 7	27 (40), 37	ns
Biochemistry				
HbA1c, %	5.8 (0.7), 19	5.9, 2	5.6 (1.4), 19	ns
UFC, μg/24 h	274 (299), 23	182 (1418), 6	250 (422), 26	ns
Serum cortisol after 1 mg DXM, μg/dL	9 (12), 23	15 (239), 5	15 (16), 33	ns
Midnight salivary cortisol, μg/L	4 (5), 10	11, 1	4 (6), 21	ns
ACTH, pg/mL	2.5 (5.0), 21	2.5 (2.5), 7	3.0 (2.9), 27	ns
Clinical evaluation				
Systolic blood pressure, mm Hg	140 (25), 21	140 (43), 5	145 (32), 29	ns
Diastolic blood pressure, mm Hg	88 (11), 21	100 (15), 5	90 (20), 29	ns
BMI, kg/m ²	27 (8), 22	27 (5), 5	29 (10), 33	ns
Prevalence of Cushing stigmata, % (n)	68 (22)	86 (7)	80 (35)	ns

Unless noted otherwise, values are median (IQR), n. Conversion from ACTH in pg/mL to SI units (pmol/L) is performed by multiplication by 0.22. Abbreviations: BMI, body mass index; DXM, dexamethasone; ns, not significant.

for a suspected renal carcinoma and surgically resected because of the suspicion of a lymph node metastasis. Histology demonstrated an adrenal macronodule.

Standardized clinical and biochemical evaluation at last follow-up

After a median follow-up of 50 months, 96% of the unilaterally adrenalectomized patients with PBMAH were clinically controlled, defined by remission of Cushing stigmata. In contrast, the percentage of biochemically controlled patients was lower, with 67% having normalized 24-hour UFC and 32% having normal cortisol suppression after 1 mg dexamethasone. UFC was 1.1-fold greater than the upper limit of normal (10% above the reference range) in patients with unilat-ADX-PBMAH (n = 13) compared with 0.5-fold in patients with unilat-ADX-CPA (n = 28, P < 0.001).

Table 2. Clinical and Biochemical Outcomes in Patients With Unilat-ADX-PBMAH and Bilat-ADX-PBMAH and Patients With Unilat-ADX-CPA

	Unilat-ADX-PBMAH, n (%)	Bilat-ADX-PBMAH, n (%)	Unilat-ADX-CPA, n (%)	P
Initial remission	21/25 (84)	9/9 (100)	39/39 (100)	0.017
Recurrence	3/21 (14)	1/9 (11) ^a	0/39 (0)	ns
Second operation necessary	3/25 (12)	1/9 (11) ^a	0/39 (0)	ns
Remission at last follow-up (according to definition) ^b				
Clinically controlled	22/23 (96)	8/9 (89)	28/38 (74)	ns
Biochemically controlled (UFC)	12/18 (67)	9/9 (100)	30/31 (97)	0.004
Biochemically controlled (DXM)	7/22 (32)	9/9 (100)	30/31 (97)	0.000

Abbreviation: DXM, dexamethasone.

^a1992 BADX, 2012 removal of a suspicious para-aortal lymph node, histologically being an adrenal adenoma.

^bClinically controlled was defined by the remission of Cushing stigmata; biochemically controlled was defined by dependence on glucocorticoid substitution and UFC <150 μg/d or cortisol after 1 mg DXM <1.8 μg/dL.

Table 3. Clinical and Biochemical Outcome in Patients With Unilat-ADX-PBMAH or Bilat-ADX-PBMAH and Patients With Unilat-ADX-CPA at Last Follow-Up

	Unilat-ADX-PBMAH (n = 20)	Bilat-ADX-PBMAH (n = 9)	Unilat-ADX-CPA (n = 38)	P
Female/male	14/6	5/4	34/4	0.039
Age at last follow-up, y	65 (11), 20	65 (29), 9	55 (24), 38	0.011
Follow-up time since operation, mo	50 (100), 20	88 (164), 9	55 (107), 38	ns
Biochemistry at follow-up				
UFC, $\mu\text{g}/24\text{ h}$	117 (133), 13	35, 3	41 (62), 28	0.003
Serum cortisol after 1 mg DXM, $\mu\text{g}/\text{dL}$	2.6 (3.1), 18	0.5, 3	1.0 (0.3), 17	0.000
Midnight salivary cortisol, $\mu\text{g}/\text{L}$	2.1 (2.3), 8	2.2, 2	0.8 (1.0), 29	0.016
ACTH, pg/mL	15 (11), 19	13 (38), 8	20 (14), 38	ns
Clinical evaluation at follow-up				
Systolic blood pressure, mm Hg	140 (20), 19	135 (26), 9	119 (26), 38	0.011
Diastolic blood pressure, mm Hg	81 (16), 19	80 (13), 9	78 (12), 38	ns
HbA1c, %	5.8 (0.8), 19	5.7 (0.9), 8	5.6 (0.6), 38	ns
Total cholesterol, mg/dL	207 (59), 19	208 (83), 8	200 (47), 38	ns
LDL, mg/dL	112 (42), 19	122 (45), 7	114 (45), 38	ns
Triglycerides, mg/dL	94 (84), 19	151 (143), 8	129 (105), 37	ns
Lowest T-value in DXA	-1.7, 3	-0.5, 3	-1.2 (1.6), 23	ns
BMI, kg/m^2	25.4 (8.6), 20	24.8 (5.7), 9	27.6 (12.0), 38	ns
Waist-to-hip ratio	0.9 (0.1), 9	1.0, 3	0.9 (0.2), 35	ns
Grip strength, % ^a	96 (29), 10	100 (29), 6	90 (38), 35	ns
Chair rising test, s	8 (5), 8	9 (5), 6	8 (4), 32	ns

Unless noted otherwise, values are median (IQR), n. Conversion from ACTH in pg/mL to SI units (pmol/L) is performed by multiplication by 0.22.

Abbreviations: BMI, body mass index; DXA, dual-energy X-ray absorptiometry; DXM, dexamethasone.

^aGrip strength was assessed with a hand dynamometer. Mean values of three trials of the leading hand were compared with median values of an age- and sex-matched normative population (= 100%).

insufficiency (58% temporary and 42% persistent at last follow-up), and all patients with bilat-ADX-PBMAH remained adrenal insufficient. Duration of temporary adrenal insufficiency was significantly shorter in patients with unilat-ADX-PBMAH compared with patients with unilat-ADX-CPA [median, 3 months (IQR, 6) vs 19 months (IQR, 45); $P = 0.002$]. The daily

hydrocortisone replacement dose at last follow-up was not significantly different between patients with bilat-ADX-PBMAH and patients with unilat-ADX-CPA [median, 25 mg/d (IQR 15) vs 20 mg/d (IQR 9); $P = \text{ns}$]. None of the patients with unilat-ADX-PBMAH experienced an adrenal crisis, whereas 38% of the patients with bilat-ADX-PBMAH and 8% of the patients

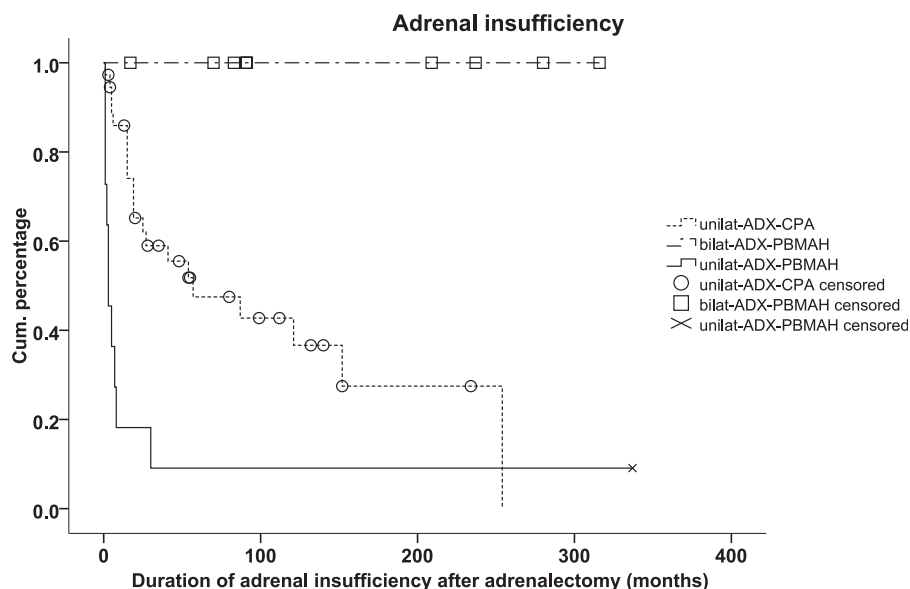


Figure 1. Kaplan-Meier analysis on adrenal insufficiency for patients with unilat-ADX-PBMAH (n = 11) or bilat-ADX-PBMAH (n = 9) and patients with unilat-ADX-CPA (n = 37).

with unilat-ADX-CPA had one crisis per year on average ($P = 0.009$).

QoL and psychiatric morbidity

QoL at last follow-up was not significantly different between the three patient groups except for general health and vitality in the SF-36 questionnaire, which was lowest in the patients with unilat-ADX-CPA (Table 4). Similarly, psychiatric morbidity was higher in patients with unilat-ADX-CPA (39% vs 16% in unilat-ADX-PMAH and 0% in bilat-ADX-PBMAH).

Surgical and long-term mortality

Surgical 30-day mortality was 0% in all groups. During follow-up, 3 of the 20 patients (15%) with unilat-ADX-PBMAH died. Causes for death were septic shock, sepsis with cardiac decompensation, and sudden death of unknown cause (each $n = 1$). All three patients had persisting biochemical hypercortisolism at last follow-up. No patients died in the bilat-ADX-PBMAH and unilat-ADX-CPA groups ($P = 0.008$) (Fig. 2). The last available cortisol level after 1 mg dexamethasone was significantly higher in the patients with unilat-ADX-PBMAH who died than in surviving patients (15.6 vs 2.4 $\mu\text{g/dL}$, $P = 0.014$).

Discussion

An increasing number of studies reported on unilateral adrenalectomy in patients with PBMAH (9–13, 22, 23). These data suggest that unilateral ADX is a safe procedure that controls hypercortisolism and avoids the risks associated with persistent adrenal insufficiency. However, several caveats have to be taken into account. The number of patients studied is still limited to seven studies with a total of 81 patients, and most reports were based on monocentric series. Moreover, there are no reference patient groups, and long-term mortality has not

been reported. These limitations prompted our study, which is multicentric and provides long-term follow-up on important clinical, biochemical, and health-related QoL parameters. In addition, the data are compared with outcome data of a closely related entity, cortisol-producing adenomas. In terms of severity of CS at time of diagnosis, our cohorts were well balanced with respect to body mass index, blood pressure, diabetes, and biochemical parameters of hypercortisolism.

Novelties of the current analysis

Our study provides substantial information relevant to patients and physicians. Clinical outcome data of our series demonstrate that unilateral adrenalectomy in patients with PBMAH results in long-term control of Cushing stigmata similar to both control groups, bilaterally adrenalectomized patients with PBMAH, and unilaterally adrenalectomized patients with CPA. Compared with both control groups, the outcome in unilaterally adrenalectomized PBMAH is *grosso modo* similar with respect to metabolic, cardiovascular, health-related QoL, and musculoskeletal parameters. However, a substantial percentage of patients with unilat-ADX-PBMAH—in our series 33% (UFC) to 68% (1 mg dexamethasone test)—keep or redevelop the endocrine phenotype of excessive cortisol secretion. Within this cohort we observed three premature casualties, in part due to infectious complications, which might be interpreted as an indicator of impaired immune function due to hypercortisolism. These patients had less controlled cortisol levels compared with the patients who were still alive at last follow-up.

Outcome of PBMAH in comparison with published series

Of the patients with unilat-ADX-PBMAH in our cohort, 84% experienced initial remission. Remission rates previously reported are similar, whereas the overall variability

Table 4. Health-Related QoL at Last Follow-up in Patients With Unilat-ADX-PBMAH and Bilat-ADX-PBMAH and Patients With Unilat-ADX-CPA at Last Follow-Up

	Unilat-ADX-PBMAH	Bilat-ADX-PBMAH	Unilat-ADX-CPA	<i>P</i>
SF-36 Physical functioning	78 (58), 6	88 (35), 4	68 (41), 18	ns
SF-36 Role-physical	63 (100), 6	88 (81), 4	0 (63), 18	ns
SF-36 Bodily-pain	61 (51), 6	63 (36), 4	44 (56), 18	ns
SF-36 General health	40 (30), 6	68 (30), 4	33 (26), 18	0.032
SF-36 Vitality	45 (39), 6	58 (19), 4	28 (28), 18	0.031
SF-36 Social functioning	57 (34), 6	94 (31), 4	38 (56), 18	ns
SF-36 Role-emotional	33 (75), 6	84 (59), 4	50 (100), 18	ns
SF-36 Mental health	50 (28), 6	86 (25), 4	52 (40), 18	ns
Cushing QoL	64 (52), 6	79 (35), 4	44 (24), 18	ns
Tuebingen CD-25 total score	22 (34), 6	15, 3	33 (30), 17	ns
Psychiatric morbidity, n (%)	3/19 (16)	0/9 (0)	15/38 (39)	0.042

Unless noted otherwise, values are median (IQR), n. For Short Form (36) Health Survey, higher scores indicate better QoL; for Cushing QoL, higher scores indicate better outcome; for Tuebingen CD-25, lower scores indicate better QoL.

Abbreviation: SF-36, Short Form (36) Health Survey.

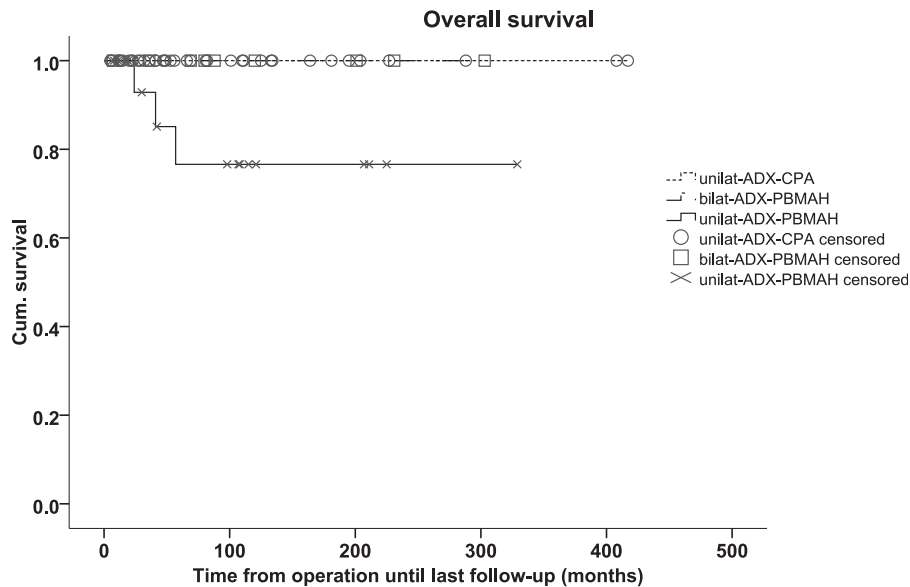


Figure 2. Kaplan-Meier analysis on overall survival for patients with unilat-ADX-PBMAH (n = 20) or bilat-ADX-PBMAH (n = 9) and patients with unilat-ADX-CPA (n = 38).

is large (25% to 93%) (9–11, 13). Contralateral adrenalectomy was performed in 12% of our initially unilaterally adrenalectomized patients with PBMAH at a later stage, compared with 0% to 33% in the literature (9–13).

In contrast to clinical outcome, biochemical outcome was less successful in our series because only 67% had normalized UFC or received glucocorticoid replacement after a median follow-up of 42 months. Normalization of UFC was superior in two studies, with 86% and 93% after a median follow-up of 53 and 69 months, respectively (11, 13). Debillon *et al.* showed normalization of UFC in all cases 3 months postoperatively but elevation of UFC after 8 years in 13% (10). Thus, it has to be taken into account that elevation of UFC might reoccur at a later stage after adrenalectomy. In accordance with Lamas *et al.* (12), we recognized elevated cortisol values after 1 mg dexamethasone and disturbed circadian salivary cortisol rhythm in 79% and 67% of cases, respectively. Abnormalities in circadian cortisol rhythm have been associated with increased risk of cardiovascular morbidity (24).

Occurrence of adrenal insufficiency was similar to the rates in published data. Of the patients with unilat-ADX-PBMAH, 50% had temporary adrenal insufficiency, 5% had persistent adrenal insufficiency, and 45% never experienced adrenal insufficiency. In the literature, the frequencies of adrenal insufficiency range from 7% to 50% (temporary), from 0% to 33% (persistent), and from 50% to 71% (absent) (10–12). Of note, 38% of the patients with bilat-ADX-PBMAH in our series had one adrenal crisis per year on average. On the other hand, long-term outcomes of bilateral adrenalectomy in patients with CS have been shown to be favorable (25).

Postoperative QoL in the SF-36 questionnaire was comparable to the postoperatively improved values of patients with unilat-ADX-PBMAH reported by Iacobone *et al.* (11).

Although the severity and duration of hypercortisolism before surgery as well as comorbidities were comparable between unilateral and bilateral adrenalectomized patients with PBMAH and patients with unilateral adenoma, mortality was significantly different. Three patients in the unilaterally adrenalectomized PBMAH group died, whereas in the other two groups no deaths occurred. In the literature mortality has not been reported, especially compared with other adrenal Cushing entities or different treatment options as bilateral adrenalectomy. We believe that our data indicate that unilaterally adrenalectomized patients with PBMAH, while being clinically asymptomatic, are at sustained risk for adverse outcome especially when biochemical parameters of autonomous cortisol secretion are greatly elevated.

Strengths and limitations

The strengths of our study include the multicentric approach, the large number of subjects; the systematic evaluation of Cushing-associated comorbidities; and the long follow-up, which allowed a mortality analysis. The limitations are largely related to the retrospective study design. Individual decisions for unilateral or bilateral adrenalectomy did not follow a predefined protocol. Some patients were lost to follow-up, and standardized evaluation of outcomes was only possible in a subgroup of patients. Moreover, the group of bilaterally adrenalectomized patients with PBMAH was much smaller than the group of unilaterally adrenalectomized patients with

PBMAH. However, considering the exceptional rarity of this condition, we are convinced that the presented data are robust enough to justify our conclusions.

Conclusions

The current study provides rare data of long-term outcome and mortality of patients with PBMAH after adrenalectomy in comparison with a reference patient group. Argumentation for acceptance of mild persistent hypercortisolism against lifelong glucocorticoid dependence is justifiable as long as it does not lead to enhanced mortality. In view of the presented data, unilateral adrenalectomy should be reserved for patients with PBMAH with asymmetric hyperplasia or mild cortisol secretion (11). Although our observational data do not allow to define a safe UFC cut-off, we believe that persistently elevated levels of more than two times upper limit of the norm should lead to additional measures to control hypercortisolism, such as adrenostatic treatment or (subtotal) contralateral adrenal surgery.

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