

Supplementary table 1. Medical therapy* used in patients with active Cushing disease grouped by mortality.

Therapy	Total n = 133	Mortality		p value
		No (n=115)	Yes (n = 18)	
Ketoconazole (200-1200 mg/day)	102 (77)	90 (78)	12 (67)	0.24
Cabergoline (0.5-3.5 mg/week)	19 (14)	18 (16)	1 (5.5)	0.46
Bromocriptine (2.5- 6.25 mg/day)	10 (7.5)	8 (7)	2 (11)	0.51
Aminoglutethimide (750-1500 mg/day)	16 (12)	12 (10)	4 (22)	0.46
Valproic acid (400-1200 mg/day)	6 (4.5)	6 (5)	0 (0%)	0.58
Others**	3 (2)	3 (3)	0 (0%)	0.41

Data presented with n and %. Statistical comparisons made with chi square or exact Fisher test. *Other therapies were not used because lack of availability in our country.

**Cyproheptadine; mitotane; fluconazole.

Supplementary table 2. Comparison of surgery, radiotherapy, or adrenalectomy and Cushing disease mortality.

Treatment	Total	Mortality		p value
		No	Yes	
	n = 133*	(n = 115)	(n = 18)	
Surgery	108 (81)	98 (85)	10 (55)	0.03
Surgery alone	56 (42)	51 (44)	5 (28)	0.10
Surgery + adrenalectomy	42 (31.5)	36 (32)	6 (35)	0.75
Surgery + radiotherapy	18 (13.5)	17 (15)	1 (5.5)	-
Adrenalectomy alone	5 (4)	3 (2.6)	2 (11)	1.0
Radiotherapy	43 (32)	40 (35)	3 (17)	0.12
Conventional	27 (20)	24 (21)	3 (17)	0.38
Gamma-knife	7 (5)	7 (6)	0 (0)	
LiNAC	9 (7)	9 (8)	0 (0)	
Radiotherapy alone	0 (0)	0 (0)	0 (0)	-
Radiotherapy + adrenalectomy	1 (0.7)	1 (0.9)	0 (0)	1.0
Surgery + radiotherapy + adrenalectomy	20 (15)	19 (16.5)	1 (5.5)	0.54
Number of treatments				
One	57 (43)	51 (44)	6 (33)	0.62
Two	38 (28.5)	33 (29)	5 (28)	
Three or more	20 (15)	19 (16.5)	1 (5.5)	

Data expressed with n (%), p value from chi square test or Fisher's exact test. *Mortality information in n= 133 patients out of 172 cases evaluated.

Supplementary table 3. Clinical and biochemical characteristics of patients with or without diabetes at diagnosis

Parameter	Total n = 168	Diabetes		p value
		No n = 94 (%)	Yes n = 74 (%)	
Women	150 (89)	84 (89)	66 (89)	1.0
Men	18 (11)	10 (11)	8 (11)	
Size				
Negative MRI	16 (10)	10 (11)	6 (9)	0.86
Microadenoma	120 (72)	65 (69)	55 (75)	
Macroadenoma	31 (19)	19 (20)	12 (16)	
Radiotherapy	44 (26)	24 (25)	20 (27)	0.17
Number of Surgeries	n = 139	n = 75	n = 64	
None	1 (0.7)	0 (0)	1 (2)	0.51
One	106 (76)	57 (76)	49 (76.5)	
Two or more	32 (23)	18 (24)	14 (22)	
Cortisol AM (mcg/ml, n= 166)	28 (21-35)	28 (20-33)	28 (23-37)	0.31
Cortisol PM (mcg/ml, n= 88)	23 (17-29)	23 (17-28)	26 (20-34)	0.09
UFC 24h (mcg/day, n=116)	494 (253-820)	510 (220-826)	470 (257-857)	0.45
ACTH (pg/ml, n=124)	56 (34-90)	50 (25-87)	60 (40-100)	0.07
Mortality	18 (11)	5 (5)	13 (17.5)	0.02

Data expressed with mean±SD (p value from student t test); median (interquartile range, p value from Mann-Whitney U test); or n (%), p value from chi square test). UFC = urinary free cortisol.

Supplementary table 4. Clinical and biochemical characteristics of patients according to cortisol reduction at afternoon at diagnosis

Characteristic	Cortisol reduction at afternoon (after 1600 h)		p value
	Lack (<40%) n=70 (%)	Preserved (≥40%) n=21 (%)	
Female	64 (91)	19 (91)	0.89
Male	6 (9)	2 (9)	
Size of adenoma			0.44
Microadenoma	52 (74)	14 (66)	
Macroadenoma	14 (20)	6 (29)	
Negative MRI	4 (6)	1 (5)	
Number of surgeries	n = 57	n = 19	0.03
None	1 (2)	0 (0)	
One	42 (74)	16 (84)	
Two or more	14 (26)	3 (16)	
Radiotherapy (n=25)	18 (72)	7 (28)	0.04
Cortisol AM (mcg/ml)	29±11.5	33±11.6	0.16
Cortisol PM (mcg/ml)	28±12	16±7.5	<0.001
Urine free cortisol 24h (mcg/day)	565 (218-1096)	436 (303-694)	0.04
ACTH (pg/ml)	69 (26-90)	57 (36-105)	0.31
Mortality	16 (23)	1 (5)	0.04

Data expressed with mean±SD (p value from independent student t test); median (interquartile range, p value from Mann-Whitney U test); or n (%), p value from chi square test).

