Pituitary (2009) 12:57–69
DOI 10.1007/s11102-007-0080-4

CASE REPORT

Malignant pituitary corticotroph adenomas: report of two cases and a comprehensive review of the literature

Agatha A. van der Klaauw · Tina Kienitz · Christian J. Strasburger · Johannes W. A. Smit · Johannes A. Romijn

Published online: 4 January 2008

Abstract Corticotroph pituitary carcinomas are tumors, defined by the presence of distant metastases that determine their poor prognosis. The diagnosis and therapy of malignant corticotroph adenomas remains a clinical challenge. The molecular mechanisms of malignant transformation of pituitary adenomas are unclear, although they are believed to arise in an adenoma-to-carcinoma sequence. We describe two cases of malignant Cushing's disease with metastases in liver and bone, respectively. The primary pituitary tumors were treated by a combination of radiotherapy and transsphenoidal surgery, but recurred several times in both patients. The time interval between the diagnosis of Cushing's disease and the discovery of metastases was 32 and 17 years, respectively. In the first case the patient died within 6 months after diagnosis of metastasis, whereas the second patient is alive at a follow-up of 2 years after the discovery of the metastasis. Furthermore, we reviewed all available cases of corticotroph pituitary carcinomas reported in the literature and analyzed their clinical features and therapeutical management. In conclusion, frequent relapses of Cushing's disease, aggressive growth of macroadenoma, Nelson's syndrome after adrenalectomy or persistently high ACTH levels should prompt the clinician to consider the possibility of pituitary corticotroph carcinomas.

Keywords Pituitary · Corticotroph adenomas · Malignant

Introduction

Pituitary carcinomas are defined by the presence of distant metastases of a pituitary tumor to the extracranial region or the cerebrospinal space [1]. Pituitary tumors in general are relatively common and are detected in about 5–10% of the normal population as incidentalomas [2]. Malignancies of the pituitary, however, are extremely rare with a prevalence of only 0.1–0.2% of all pituitary tumors [3, 4]. The true frequency of pituitary carcinomas may be slightly underestimated, because metastatic lesions have often been diagnosed at post-mortem examination and meanwhile more sensitive imaging techniques have become available [5, 6].

Most pituitary carcinomas are endocrinologically active [3, 7]. In addition, the number of reported non-functioning cases might be overestimated, especially when reported before the routine use of immunohistochemistry [8] and ultrasensitive hormone assays. Although ACTH-producing pituitary tumors present only a minority of all pituitary adenomas [9], they account for 40% of all pituitary carcinomas [3, 7, 10].

Reliable predictive markers for malignant transformation of a pituitary tumor have not been identified so far [1]. Therefore, the initial diagnosis of malignant pituitary Cushing's disease remains a clinical challenge. Indicators of potential malignancy of ACTH producing adenomas are major increases in pituitary tumor volume along with

A. A. van der Klaauw and T. Kienitz contributed equally to this study.

A. A. van der Klaauw (✉) · J. W. A. Smit · J. A. Romijn
Department of Endocrinology and Metabolism, C4-R, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands
e-mail: a.a.van_der_klaauw@lumc.nl

T. Kienitz · C. J. Strasburger
Clinical Endocrinology, Department of Internal Medicine, Gastroenterology, Hepatology and Endocrinology, Charité University Medicine Campus Mitte, Berlin, Germany

persistently high plasma ACTH and cortisol levels. It is possible that bilateral adrenalectomy in Cushing's disease might trigger the development of pituitary carcinoma, just like the stimulation of growth of the pituitary in Nelson's syndrome.

In previous reviews, non-uniform definitions of pituitary carcinoma caused confusion by designating invasive pituitary adenomas as malignant or including pituitary carcinomas without evidence of metastasis [6, 11]. Furthermore, metastases to the pituitary gland were sometimes not discriminated from primary pituitary carcinoma [12]. At our outpatient clinic two patients presented with ACTH-producing pituitary carcinoma resulting in malignant Cushing's disease (CD). The difficult management of this entity prompted us to provide a detailed analysis of our two cases and a systematic review of the literature, which is the largest review so far. Therefore, we searched for previous case reports on malignant corticotroph adenomas in the Pubmed library using the keywords "ACTH, corticotroph; pituitary, hypophysis; adenoma, carcinoma, adenocarcinoma; malignant, metastasis". In addition, we analyzed previous reviews reporting on pituitary carcinomas in general without detailed analysis of the corticotroph subentity. The literature search was completed on September 30, 2006.

Case report

Case 1 (Fig. 1)

A 19-year-old man was in good health until he suffered a contusion during military training in November 1960. In 1961 an X-ray of the sella was made for persisting headaches which showed sellar enlargement. In the summer of 1963 symptoms of hypercortisolism evolved with fatigue, easy bruisability, striae and weight gain of 15 kg. In 1964, he was diagnosed with Cushing's disease due to a pituitary macroadenoma. Cushing's disease was diagnosed by increased cortisol production rate (109 mg/24 h, normal value < 12 mg/24 h) and elevated excretion of 17-ketogenic steroids (29.8–67.4 mg/24 h, normal values < 20 mg/24 h). In addition, serum cortisol was insufficiently suppressed by 1 mg dexamethasone. Therapy consisted of conventional external pituitary radiotherapy with 30 Gy in October 1964. Within 3 months clinical signs and symptoms of Cushing's disease resolved, with normal anterior thyreotrophic function but hypogonadotrophic hypogonadism. Subsequent biochemical evaluation revealed normal values for urinary secretion of 17-ketosteroids and 17-ketogenic steroids, and cortisol production rate was within the reference range in 1965. During the following years the patient remained in remission. In 1982, CT-imaging of the pituitary region revealed an empty sella. In 1987, however, the patient reported weight gain of 10 kg in 2 years and easy bruising. On physical examination a buffalo hump, central adiposity, moon-face, bruises, atrophic skin, and striae were noticed. Biochemical evaluation revealed insufficient suppression on dexamethasone 1 mg overnight (300 nmol/l, normal suppression <100 nmol/l). Twenty-four hour urinary cortisol excretion was 700 nmol/24 h (upper normal value 220 nmol/24 h). CT-imaging of the pituitary revealed tumor growth with extension into the right cavernous sinus and in the sphenoid sinus (Hardy–Wilson classification III-E). Ketoconazole was started with increasing dosages prior to transsphenoidal surgery in November 1987 followed by

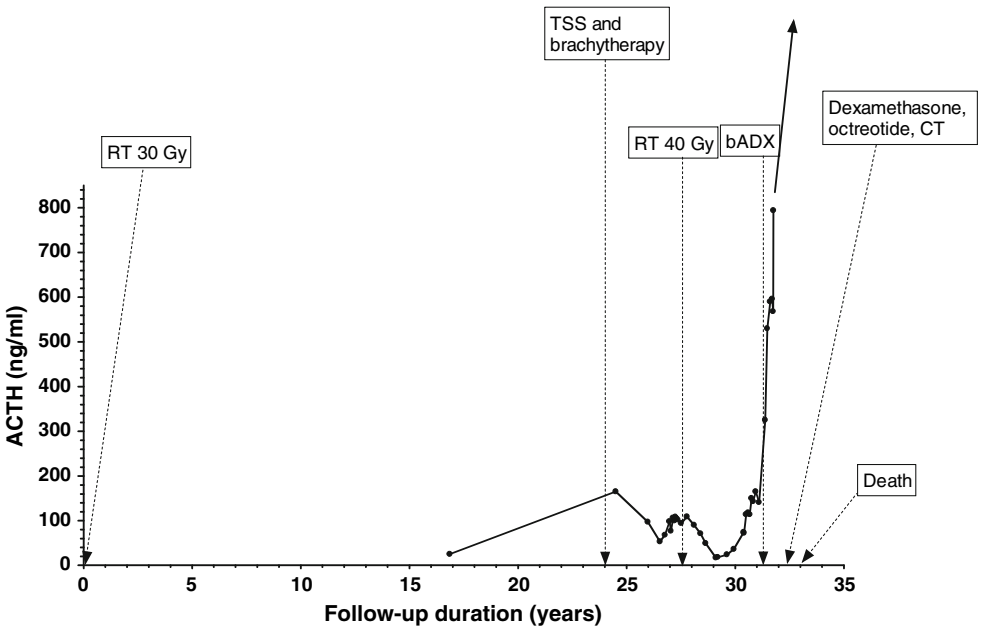

Fig. 1 Clinical course in case 1. bADX bilateral adrenalectomy; CT chemotherapy; RT radiotherapy; TSS transsphenoidal surgery

brachytherapy with I-125 (four implants with a total activity of 0.55 mCi). The postoperative course was complicated by a liquor leak and subsequent meningitis due to *Staphylococcus aureus*. Histological examination of the tumor revealed positive immunostaining for ACTH with occasional mitotic figures and polymorphic nuclei. Clinical signs and symptoms of Cushing's disease regressed and 24 h urinary cortisol excretion normalized (110 nmol/24 h). In 1990, however, our patient presented with diplopia due to a right-sided abducens nerve paresis and clinical signs and symptoms of recurrent Cushing's disease, which developed within a few months. Neurological examination also revealed discrete paresis of the right-sided trigeminal nerve. The diplopia was caused by tumor extension into the right cavernous sinus on MRI. Biochemical evaluation revealed 24 h urinary cortisol excretions between 500 and 800 nmol/24 h. Fractionated conventional radiotherapy was administered by a linear accelerator in a total dose of 40 Gy. Diplopia regressed after radiotherapy and ACTH concentrations gradually decreased from 108 ng/l during radiotherapy to 49 ng/l in January 1992. Urinary 24 h cortisol secretion decreased to 79 nmol/24 h. In 1992, MRI revealed a significant decrease in pituitary tumor volume. In 1993, the patient developed recurrent Cushing's disease, nonetheless. Biochemical evaluation revealed increased 24 h urinary cortisol excretion (1860 nmol/24 h) and insufficient suppression to dexamethasone (serum cortisol 100 nmol/l after 0.5 mg dexamethasone four times daily during 2 days (normal values < 60 nmol/l), and ACTH 28 ng/l). In October 1993, diplopia recurred, now due to right-sided trochlear nerve paresis. MRI revealed tumor progression with extension into the right cavernous sinus, in the right prepontine cisterna and in the course of the trochlear nerve. In January 1994, ketoconazole was started at a dose of 200 mg three times a day, but total 24 h urinary cortisol excretion remained increased. MRI in 1995 revealed progression of the pituitary tumor. Clinically, the patient gained weight again and developed diabetes mellitus for which insulin was started. Bilateral adrenalectomy was performed in February 1995. Pathological examination revealed bilateral adrenal hyperplasia (right adrenal gland 35 g, left adrenal gland 20 g). Glucocorticoid and mineralocorticoid substitution therapy were started and insulin treatment could be stopped. After bilateral adrenalectomy the pituitary tumor showed progressive growth during 1995 with increasing ACTH concentrations (586 ng/l directly after bilateral adrenalectomy to 396,000 ng/l in August 1995) and a strong pigmentation of the skin developed, compatible with Nelson's syndrome. High-dose dexamethasone treatment was started (1.5 mg daily). ACTH levels decreased subsequently eightfold. However, progressive neurological deficits due to local pituitary tumor growth developed with paresis of n. II, III, V and VI on the right side and n. VI on the left side. Somatostatin analog therapy (octreotide) was started at a dose of 500 mg three times daily. There were also multiple echo-dense lesions in the liver. Pathological examination of one of these lesions revealed a neuro-endocrine tumor positive for ACTH. Extended MRI of the cerebrum and the spinal cord revealed no metastases. No metastases were found in the lungs. In August 1995 chemotherapy was started with doxorubicin 45 mg/m^2 i.v. on day 1, in combination with cyclophosphamide 1,000 mg/m^2 i.v. on day 1 and etoposide 100 mg/m^2 i.v. on day 1, 3 and 5. After the second course of chemotherapy the patient developed ulcers on arms and in the perianal region. Surgery was necessary to clean the ulcers and remove the debris. The condition of the patient worsened subsequently. In January 1996 the patient and the treating physicians decided to stop active treatment and to continue with palliative care. The patient died the same month.

Autopsy revealed an ACTH-positive pituitary tumor of 2 cm on the right side of the sella and partial empty sella at the left side, extensive diffuse liver metastases (liver weight 3,750 g, normal weight 1,500 g), metastases in the thoracic and lumbar vertebra, and trivascular coronary atherosclerosis with stenosis of RCA and LCA to 75%. DNA-analysis of the pituitary tumor and metastases in the liver showed DNA-aneuploid lines with a DNA-index of 0.67 and 0.68 which is a strong indicator for genetic relationship of the two specimens.

Case 2 (Fig. 2)

In 1989, a 35-year old man was diagnosed with Cushing's disease due to a pituitary macroadenoma (Hardy–Wilson classification II-B-D-E) with bitemporal hemianopsia. The diagnosis was based on typical signs and symptoms of Cushing's disease as well as biochemical abnormalities (17-ketogenic steroids excretion 149 mg/24 h, normal values < 20 mg/24 h). He underwent transsphenoidal surgery which was complicated by a worsening of the visual field defects due to a hematoma of the optic chiasm. He therefore underwent an additional transcranial exploration. Pathological examination revealed an ACTH-producing adenoma with sporadic mitotic figures and polymorphic nuclei. Because of residual tumor with extension into the suprasellar area and the cavernous sinus as well as persistent biochemical abnormalities (17-ketogenic steroids 42 mg/24 h), additional pituitary irradiation (45 Gy) was given. Subsequently, visual fields improved together with tumor regression on MRI. Biochemical regression, however, was insufficient indicated by serum cortisol level of 0.19 μg/l after 1 mg dexamethasone overnight. In 1991, hypogonadism was diagnosed (Testosteron 4.1 nmol/l, normal values > 8 nmol/l) for which the patient received

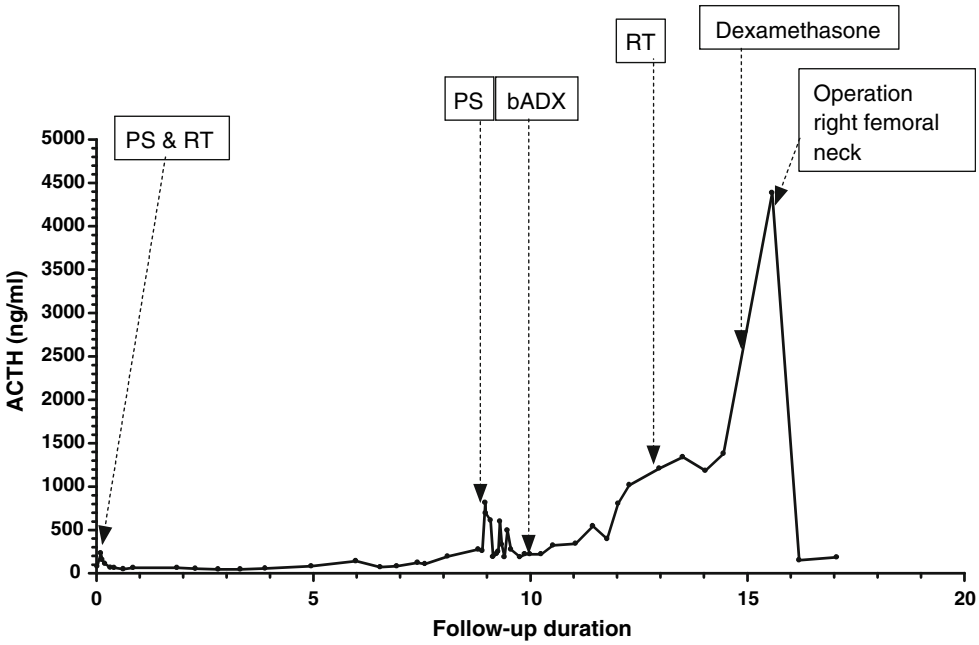

Fig. 2 Clinical course in case 2. bADX bilateral adrenalectomy; PS Pituitary surgery; RT radiotherapy

testosterone replacement. In 1992, secondary hypothyroidism developed (free T4 9.1 pmol/l, normal) for which thyroxine replacement was started. In 1998, recurrent Cushing's disease was diagnosed by clinical signs and excessive 24-h urinary cortisol excretion (3,800 nmol/24 h) and ACTH levels of 693 ng/l. MRI revealed a dorsolateral sellar tumor mass with extension into the clivus and the sphenoid sinus. The patient underwent transsphenoidal reexploration during which residual adenoma tissue was removed. Nonetheless, hypercortisolism persisted and a bilateral adrenalectomy was performed. After this procedure the patient was treated with hydrocortisone (25 mg/day) and fludrocortisone (0.1 mg/day). In 2002, ACTH levels were further increased (1017 ng/l) and MRI showed growth of the sellar tumor remnant. Therefore, the patient was treated with additional fractionated stereotactic irradiation (total dose 45 Gy). In 2004, MRI revealed a clear regression of the tumor mass. ACTH levels, however, continued to progress with a level of 1377 ng/l in 2004. Therefore, dexamethasone 1.25 mg/day was given. In 2006, despite absence of tumor progression on sellar MRI serum, ACTH levels increased to 4384 ng/l and the patient developed hyperpigmentation of the skin. Meanwhile, the patient had developed pain in the right upper leg. X-ray and subsequent MRI of the right femoral neck revealed a mass (diameter 10 cm) with extension into the soft-tissue. Biopsy revealed tumor tissue, strongly positive for ACTH. CT scans of chest and abdomen did not reveal any other tumor localizations. Scintigraphy with In-111 octreotide revealed increased uptake in the right femoral neck. Although other therapies including external irradiation were considered, the patient underwent a surgical removal of the right femoral neck. Pathological examination revealed a complete removal of the tumor. Postoperatively, ACTH levels dropped to 150 ng/l. Up to now, our patient is in stable condition and regularly visiting the outpatient clinic for follow-up visits (Fig. 2).

Discussion

These two case reports highlight several phenomena of malignant Cushing's disease. The patients can present with Cushing's disease without any signs of metastases at initial presentation. There can be a long delay between initial presentation and suspicion of malignant disease (23 and 9 years, respectively). Finally, survival is long after initial diagnosis of Cushing's disease (32 and 18 years, respectively).

In addition to our 2 cases, only 56 previous cases of malignant corticotroph adenomas have been reported, summarized in Table 1. The first case was reported in 1936 [16]. Sixty-six percent of the cases were female (Table 2), whereas in Cushing's disease in general approximately 80% is female [49]. Mean age at presentation was 39 years (range 13–71 years). Cushing's syndrome was present in 64% at presentation, whereas 26% of patients presented with visual complaints due to a silent corticotroph adenoma. It should be noted that in 10% of cases initial signs and symptoms at presentation were not documented. Initial therapy consisted of transsphenoidal or transcranial surgery (74%), (postoperative) radiotherapy (50%), unilateral (4%) and bilateral adrenalectomy (28%), and drug therapy (56%,

Table 1 Review of reported cases of malignant Cushing's disease

Author, year of publication	Sex	Age	Presentation	Initial treatment	Number and treatment for local pituitary recurrences	Time interval diagnosis-metastases (years)	Metastatic sites	Treatment of metastases	Outcome	Time interval metastases-death (years)
Ahmed 2000 [12]	F	44		TSS, RT		2	Cervical lymph node	Surgery, SSI	Still alive at publication	
Ahmed, 2000 [12]	M	26	CS	bADX, RT	1 (TSS)	3.46	Liver, intracranial	SSI	Death due to disease	5.04
Bates, 1995 [13]	M	30	Visual field defects	PS	2 (PS, PS)	8	Intracranial	RT, bADX, SSI	Death due to disease	2
Casson, 1986 [14]	M	58	CS	PS, bADX	2 (PS, RT)	6	Sternum, liver, lymph node		Death due to acute paraparesis due to spinal metastases	Death shortly after diagnosis of metastases
Ceyhan, 2006 [15]	F	60	CS	TSS, RT	3 (2 recurrences before metastases: treatment not documented, 1 recurrence at time of metastasis: RT)	6	Cervical vertebrae, epidural component	Surgery	Still alive at publication	
Cohen, 1936 [16]	F	45	CS	RT		7	Liver		Death due to bronchopneumonia	Metastases found in post-mortem analysis
Della Casa, 1997 [17]	F	52	Visual complaints	TSS, RT	1 (now clinical CS; TCS, RT)	11	Intracranial, spinal dissemination	Craniotomy; SSI, OCT, cyproheptadine, bromocriptine, sodium valproate (all during 2 months: no effects); SSI: partial suppression	Death due to disease	3
Farrell, 2003 [18]	F	34	Visual field defects	TSS, RT	1 (now clinical CS; TSS: 2 times debulking, RT, bADX)	5	Cervical vertebrae, lumbar spine, ribs, pelvis	RT, OCT, CT (carboplatin, etoposide and vincristine)	Death due to disease	1
Feiring, 1953 [19]	F	31	CS	RT	6 (RT; TCS & RT; RT; TCS &RT; RT; RT)	6	Intracranial (dura)		Death due to rupture of mycotic aneurysm of the abdominal aorta	Metastases found in post-mortem analysis
Forbes, 1947 [20]	F	42	CS	RT	1 (brachytherapy, PS)	3	Liver		Death due to bronchopneumonia	Metastases found in post-mortem analysis
Frost, 1995 [8]	F	33		PS, RT	1 (recurrence at time of metastasis: TSS)	6	Intracranial, intradural (extracranially)	Surgery, CT	Still alive at publication	
Gabrilove, 1984 [11]	M	37	CS	bADX	1 (Nelson's, cobalt teletherapy)	4.83	Spinal cord, cauda equina, heart, liver, pancreas, bone		Death due to disease	Death shortly after diagnosis of metastases
Gaffey, 2002 [21]	F	56	CS	TSS, bADX	2 (RT, stereotactic gamma knife surgery)	6	Liver	Surgery, OCT, CT (8 courses cyclophosphamide, vincristine, dacarbazine)	Still alive at publication	

Table 1 continued

Author, year of publication	Sex	Age	Presentation	Initial treatment	Number and treatment for local pituitary recurrences	Time interval diagnosis-metastases (years)	Metastatic sites	Treatment of metastases	Outcome	Time interval metastases-death (years)
Gaffey, 2002 [21]	F	35	CS	TSS	1 (TSS, bADX, RT)	11	Intracranial, spine	Craniotomy	Death due to carcinomatous meningitis	4
Gaffey, 2002 [21]	F	63	CS	bADX	1 (Nelson's, TSS)	8	Intracranial (dura)	Surgery, RT	Still alive at publication	
Gaffey, 2002 [21]	F	17	NFA	PS, RT	3 (PS, PS, PS)	12	Bone	RT	Still alive at publication	
Garrao, 1997 [22]	F	47	CS	bADX	1 (TSS, RT)	14.25	Bone	Surgery, OCT	No anatomical cause for death	0.42
Gatti, 1984 [23]	F	13	CS	lADX, RT	3 (RT, RT & rADX, TSS)	19	Intracranial		Death due to hemorrhagic brain insult due to metastasis	Death shortly after diagnosis of metastasis (few hours after imaging hemorrhagic brain insult)
Heukamp, 2004 [24]	F	40	Silent pituitary tumor	PS	2 (PS, PS)	16	Intracranial	2 times surgery, stereotactic RT	Still alive at publication	
Hinton, 1998 [25]	F	53	CS	TSS, RT		0.75	Liver, bone	CT, surgery	Death due to disease	0.42
Holthouse, 2001 [26]	F	17	Headache	PS	2 (during 1st pregnancy: high dose dexamethasone & bromocriptine, after delivery PS, RT; TSS)	11	Bone	RT, craniotomy	Still alive at publication	
Kaiser, 1983 [27]	F	17		PS, RT, bADX		5.58	Bone, liver, lung, mediastinum	CT (cyclophosphamide, adriamycin, 5-fluorouracil)	Still alive at publication	
Kaltsas, 1998 [5]	M	41	CS	PS, RT, bADX, CT started without evidence of peripheral metastases (lomustine/5-FU (6 cycles), carboplatin (6 cycles), dacarbazine (2 cycles))			Spine, liver		Death due to disease	1.5
Kemink, 1999 [28]	F	22	CS	bADX	3 (TCS, cyproheptadine, TCS & RT)	34	Intracranial (dura)		Death due to purulent leptomeningitis	Metastasis found in post-mortem analysis

Table 1 continued

Author, year of publication	Sex	Age	Presentation	Initial treatment	Number and treatment for local pituitary recurrences	Time interval diagnosis-metastases (years)	Metastatic sites	Treatment of metastases	Outcome	Time interval metastases-death (years)
Kouhara, 1992 [29]	M	15	CS	bADX	3 (Nelson's, TSS, TSS, RT)	24	Intracranial, spine	Surgery: metastases of intraspinal space	Still alive at publication	
Landman, 2002 [30]	F	14	CS	bADX	1 (Nelson's, TCS)	14	Intracranial	2 times craniotomy	Still alive at publication	
Levesque, 1991 [31]	M	25	CS	TSS, RT, OP'DDD		2.5	Intracranial (dura), lymph node	Meningeal, cervical surgery, OP'DDD	Death due to intracranial hypertension due to metastasis	0.5
Lormeau, 1997 [32]	F	18	CS	PS	5 (bADX & PS, RT, TCS, RT, PS)	7.58	Liver	2 times hepatic chemoembolization	Still alive at publication	
Masuda, 1999 [33]	M	59	Headache, decreased visual acuity	TSS, RT		1.5	Dura, intracranial, lungs, lymph nodes		Death due to cardiac arrest	Death shortly after diagnosis of metastasis
Moore, 1976 [34]	M	21	CS	RT, bADX, PS		15	Intracranial, spinal cord, liver		Death due to disease	Metastases found in post-mortem analysis
Nawata, 1990 [35]	M	53	Diplopia, decreased visual acuity	TSS, RT	1 (now clinical CS, TCS, RT)	4	Intracranial, liver, lung	OP'DDD, CT	Death due to disease	Death shortly after diagnosis of metastasis
Nosé-Alberti, 1998 [36]	F	21	CS	TSS, rADX		1.33	Liver		Death due to sepsis (4 months after initial TSS)	Metastases found in post-mortem analysis
Papotti, 1984 [37]	F	13	CS	lADX, brachytherapy	5 (brachytherapy, brachytherapy & rADX, PS, PS, RT)	19	Intracranial, dura		Death due to cerebral bleeding	Death shortly after diagnosis of metastasis (1 h post-imaging of bleeding)
Pernicone, 1997 [3]	F	65		TCS		5	Spinal subarachnoid	Surgery, RT	Death due to disease	1.5
Pernicone, 1997 [3]	M	71		RT, sphenoid biopsy		3.5	Lymph node, muscle	ADX	Death due to disease	0.25
Pernicone, 1997 [3]	F	69		TCS, RT		11	Intracranial, spinal subarachnoid	RT	Death due to disease	1
Pernicone, 1997 [3]	F	48		RT		18	Bone	RT	Still alive at publication	
Pernicone, 1997 [3]	M	37		TCS, RT		17	Spinal subarachnoid, liver	Surgery, RT	Death due to disease	7 days
Pernicone, 1997 [3]	M	70	CS	TCS		8	Dura cranial/spinal	RT	Death due to disease	0.5
Queirox, 1975 [38]	F	36	CS	bADX			Liver		Death due to postoperative shock after bADX	Metastases found in post-mortem analysis

Table 1 continued

Author, year of publication	Sex	Age	Presentation	Initial treatment	Number and treatment for local pituitary recurrences	Time interval diagnosis-metastases (years)	Metastatic sites	Treatment of metastases	Outcome	Time interval metastases-death (years)
Richter, 2000 [39]	F	49	CS	TSS	4 (now clinical CS; PS, bADX & RT, PS, RT)	8	Liver, bone	RT of bone metastases	Still alive at publication	
Roncaroli, 2003 [40]	M	26	Visual impairment	PS, RT		2	Intracranial (dura)		Death due to disease	21
Roncaroli, 2003 [40]	F	58	Blindness right eye	TCS, RT	1 (bADX)	5	Intracranial		Death due to disease	13
Roncaroli, 2003 [40]	M	48	Left temporal hemianopsia	TCS, RT		0.25	Skin, lymph node		Death due to disease	1.75
Roncaroli, 2003 [40]	F	35	Headache, visual impairment	TSS, RT		4	Bone		Death due to disease	2.67
Roncaroli, 2003 [40]	F	28	Headache, visual field reduction	TCS, RT		15	Intracranial, oral cavity		Death due to myocardial infarction	1
Salassa, 1959 [41]	M	41	CS	bADX	3 (Nelson's; TCS, RT, RT)	4.5	Spinal cord, liver		Death due to disease	0.5
Scheithauer, 2001 [42]	F	59	CS	PS, bADX		7	Liver	Segmental hepatectomy	Still alive at publication	
Scheithauer, 2001 [42]	F	17	CS			11	Bone	CT, RT	Still alive at publication	
Scheithauer, 2001 [42]	F	35	CS	PS, bADX		12	Intracranial, spinal meninges	Craniotomy	Death due to disease	4
Sheldon, 1954 [43]	F	26	CS			2.08	Liver		Death during preparation for exploratory surgery of adrenals	Metastases found in post-mortem analysis
Singh, 2000 [44]	F	20	Acromegaly	TSS	2 (RT & PS, 2nd recurrence: now signs and symptoms of acromegaly & CS)	1	Liver	Ketoconazole	Death due to thromboembolism	0.08
Suzuki, 2002 [45]	F	61	Bitemporal hemianopsia	TS	1 (now clinical CS, RT)	6.33	Liver	SSI	Still alive at publication	
Tonner, 1992 [46]	F	52	CS	TCS, RT		3	Intracranial	Ketoconazole	Death due to disease	0.75
Zafar, 1984 [47]	M	56	CS	TCS, RT	1 (refusal of PS, ketoconazole/ aminogluthetamide/ OP'DDD)	5	Intracranial, spinal meninges		Death due to pneumonia	Metastases found in post-mortem analysis

Table 1 continued

Author, year of publication	Sex	Age	Presentation	Initial treatment	Number and treatment for local pituitary recurrences	Time interval diagnosis-metastases (years)	Metastatic sites	Treatment of metastases	Outcome	Time interval metastases-death (years)
Zahedi, 2001 [48]	F	40	CS	TSS, RT	1 (after diagnosis of metastasis; TSS & RT & bADX)	5	Lymph node	Resection of lymph node	Still alive at publication	
Van der Klaauw and Kienitz, 2007	M	23	CS	RT	3 (TSS & brachytherapy, RT, bADX)	32	Liver, bone	CT	Death due to disease	0.5
Van der Klaauw and Kienitz, 2007	M	35	CS	TSS (TCS due to hematoma), RT	2 (PS & bADX; RT)	17	Bone	Surgery	Still alive at publication	

bADX bilateral adrenalectomy; lADX left adrenalectomy; rADX right adrenalectomy; CS Cushing's syndrome; CT chemotherapy; Non-functioning adenoma (NFA) [21]; OCT octreotide; PS pituitary surgery; RT radiotherapy; SSI steroid synthesis inhibitors; TCS transcranial surgery; TSS transsphenoidal surgery

ketoconazole, octreotide, OP'DDD, and steroid synthesis inhibitors).

In our first case, Cushing's disease recurred three times after initial cure for which he was treated with transsphenoidal surgery and brachytherapy, radiotherapy and bilateral adrenalectomy, respectively. In our second case, Cushing's disease recurred two times for which the patient was treated by transsphenoidal surgery, bilateral adrenalectomy, and radiotherapy. Recurrences of Cushing's disease were reported frequently in the other case reports of malignant Cushing's disease; one recurrence was reported in 15 patients [8, 11, 12, 17, 18, 20–22, 30, 34, 35, 40, 45, 47, 48], two recurrences in 7 patients [13, 14, 21, 24, 26, 44] and three or more recurrences in 10 patients [15, 19, 21, 23, 28, 29, 32, 37, 39, 41]. Nelson's syndrome, defined as pituitary tumor progression after bilateral adrenalectomy, developed in one of our patients. Bilateral adrenalectomy was performed as initial treatment in 16 cases (28%) after which recurrent Cushing's syndrome due to growth of the pituitary was documented in 11 cases [11, 12, 14, 21, 22, 28–30, 34, 41]. Pituitary tumor recurrences after bilateral adrenalactomy during the course of the disease, were reported in only 4 other patients [23, 32, 37, 39].

The time interval between primary diagnosis of Cushing's disease and diagnosis of metastases was 32 and 17 years, respectively, which is relatively long compared to the mean interval of 8.8 years with a range of 0.25–34 years in the previously reported cases. Presenting symptoms of metastases were mainly dependent on the localization of metastases. A few metastases were asymptomatic and only found during routine follow-up screening for (recurrent) Cushing's disease [12, 13, 23, 46]. Most of the metastases, however, caused problems such as pain or local compression due to local growth in liver [12, 21, 25, 27, 32, 39, 45], bones [8, 11, 14, 18, 26, 35], and the central nervous system [15, 17, 21, 22, 24, 29–31]. In nine cases metastases were found only by post-mortem analysis in the liver, intracranial, meninges, and spinal cord [16, 19, 20, 28, 34, 36, 38, 43, 47]. Within the central nervous system, metastatic sites were intracranial in 43%, and extracranial in 24%. Extramedullary metastases (62% of the cases) were mostly reported in the liver [3, 11, 12, 14, 16, 20, 21, 25, 27, 32, 35, 36, 39, 41–45], lymph nodes [3, 12, 31, 40, 48], and bone [3, 11, 14, 18, 21, 22, 25–27, 39, 40, 42].

In 8 cases including one of our cases, metastases were found solely in bone, of which 4 patients were still alive at time of report in the literature [21, 26, 42]. Those patients had been treated with surgery (our case, [15]), with radiotherapy [21, 26], and with combined chemotherapy and radiotherapy [26]. Time interval to death in the other four cases ranged from 0.4 to 2.7 years [3, 15, 22, 40].

Table 2 Summary of clinical features of the reported cases of malignant Cushing's disease

Characteristics ($n = 58$)		
Gender, male (n (%))		19 (33)
Age (years)		39 (13–71)
Presentation (n (%))	Cushing's syndrome	37 (64)
	Visual complaints, silent adenoma	15 (26)
	Not documented	6 (10)
Initial therapy (n (%))	Transsphenoidal or transcranial surgery	43 (74)
	Radiotherapy	29 (50)
	Uni-/bilateral adrenalectomy	2 (3)/16 (28)
	Medicamentous therapy[a]	9 (16)
Metastatic sites (n (%))	Intracranial central nervous system	25 (43)
	Extracranial central nervous system	14 (24)
	Extramedullary	36 (62)
Mean time interval diagnosis-metastases (years)		8.8 (0.25–34)
Mean interval metastases-death (years)		1.7 (0–21)
Alive at publication (n (%))		18 (31)

[a] Steroid synthesis inhibitors, octreotide, OP'DDD, chemotherapy (in 1 case)

In 10 cases, metastases were found only in the liver [16, 20, 21, 32, 36, 38, 42–45]. Of those patients, two were still alive at publication. One patient, a 56-year-old woman at diagnosis, was treated by resection of liver metastases and 8-cycle chemotherapy (cyclophosphamide, vincristine, dacarbazine) and still alive after almost 2 years after diagnosis of liver metastases [21]. The other patient, 18-year-old woman at diagnosis, was treated by hepatic chemo-embolization (cisplatin, lipiodol and spongel power) and was still alive after almost 2.5 years after diagnosis of liver metastases [32].

Of our patients, one patient was still alive at publication, but the other patient died 6 months after the diagnosis of metastases. Of all reported cases, 18 patients (31%) were still alive at publication of the data with a follow-up after initial presentation of 0–7 years after the diagnosis of metastases; four with solitary liver metastases [21, 32, 42, 45], two with multiple sites of metastases [27, 39], five with solitary bone metastases (our case, [15, 21, 26, 42]) as discussed above. The other patients had solitary lymph node metastases ($n = 2$) which were extirpated [12, 48] or metastases in the central nervous system ($n = 5$) for which surgery [8, 24, 29, 30], or combined surgery and radiotherapy was applied [21]. However, the mean interval between diagnosis of metastases and death was 1.7 years with a range of 0–3.9 years. Survival after the initial presentation is approximately 10 years, which is comparable to the survival in patients with a malignant prolactinoma [50]. However only 33% of all reported cases with malignant CD survived more than 1 year after the development of metastases.

Malignant pituitary tumors are thought to arise from initially benign, large macroadenomas [51]. The mechanisms underlying malignant transformation are incompletely understood [51] and prediction of future malignant behavior of ACTH-producing pituitary adenomas is not possible until now. Frequent recurrences of pituitary adenomas might be indicative of a non-benign course. In the reported cases CD recurred at least one time in 55% of cases. However, recurrence of benign Cushing's disease after initial surgical cure also occurs in 5–36% of the patients during long-term follow-up [52–57]. Furthermore, growth of the pituitary tumor occurred in 67% of the reported cases that were treated with bilateral adrenalectomy as primary treatment. The prevalence of Nelson's syndrome without evidence of distant metastases of the pituitary tumor ranges from approximately 30–50% [58, 59] in adrenalectomized patients and thus seems rather high in the reported cases with malignant pituitary CD. Therefore adrenalectomy might trigger transformation of a pituitary tumor in an adenoma-to-carcinoma sequence. Nevertheless, prophylactic irradiation of the pituitary to prevent Nelson's syndrome has not been proven to be effective and remains controversial [60, 61].

In addition, in one third of the reported cases the initial presentation consisted of mass effects of a silent adenoma and Cushing's syndrome evolved only in the course of the disease. This is in contrast with findings of Scheithauer et al. [62] who report 23 cases with a benign silent corticotrophic adenoma at pathology reports, but in these cases no symptoms of hypercortisolim occurred during the course of the disease. Although data are scarce, the evolvement of Cushing's syndrome after initial presentation of a silent corticotrophic adenoma might thus be considered as indicative of possible future malignant behaviour of the pituitary tumor.

Persistently high ACTH levels despite various treatments targeted at the pituitary should prompt the clinician to

consider possible malignant pituitary CD. Most of the metastases, however, caused local signs or symptoms such as pain located in the bones or abdomen (as in our two cases) and radiological investigations to detect metastatic disease should be preferably targeted on the basis of clinical findings. Occasionally, intracranial metastatic disease was found on routine radiological scanning of the pituitary tumor.

There is case-to-case variability of the effect of chemotherapy on prognosis. Although these data involve only a limited number of patients, we conclude that chemotherapy does not improve prognosis of malignant corticotroph adenoma. In addition, octreotide therapy [17, 18, 21, 22], cyproheptadine [30], and OP'DDD [31, 35] were tried. Survival in these patients was not different from other patients. Thus, it seems that surgical removal of metastases might provide the best chance of survival. Molecular mechanisms underlying malignant transformation of pituitary adenomas are incompletely understood until now, but could present targets for development of new drugs to control malignant pituitary CD.

In conclusion, malignant pituitary CD is very rare. Frequently recurring CD, invasive macroadenoma, Nelson's syndrome or persistently high ACTH levels should prompt the clinician to consider the possibility of malignant disease. Diagnosis of malignancy at an early point in time might allow aggressive local and systemic therapy to improve prognosis significantly.

Acknowledgements A.A. van der Klaauw is supported by an AGIKO grant of the Netherlands Organisation for Health Research and Development (grant number: 92003423).

References

1. Kovacs K, Scheithauer BW, Horvath E, Lloyd RV (1996) The World Health Organization classification of adenohypophysial neoplasms. A proposed five-tier scheme. Cancer 78:502–510
2. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH (1994) Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 120:817–820
3. Pernicone PJ, Scheithauer BW, Sebo TJ, Kovacs KT, Horvath E, Young WF Jr, Lloyd RV, Davis DH, Guthrie BL, Schoene WC (1997) Pituitary carcinoma: a clinicopathologic study of 15 cases. Cancer 79:804–812
4. Pichard C, Gerber S, Laloi M, Kujas M, Clemenceau S, Ponvert D, Bruckert E, Turpin G (2002) Pituitary carcinoma: report of an exceptional case and review of the literature. J Endocrinol Invest 25:65–72
5. Kaltsas GA, Mukherjee JJ, Plowman PN, Monson JP, Grossman AB, Besser GM (1998) The role of cytotoxic chemotherapy in the management of aggressive and malignant pituitary tumors. J Clin Endocrinol Metab 83:4233–4238
6. Lubke D, Saeger W (1995) Carcinomas of the pituitary: definition and review of the literature. Gen Diagn Pathol 141:81–92
7. Ragel BT, Couldwell WT (2004) Pituitary carcinoma: a review of the literature. Neurosurg Focus 16:E7
8. Frost AR, Tenner S, Tenner M, Rollhauser C, Tabbara SO (1995) ACTH-producing pituitary carcinoma presenting as the cauda equina syndrome. Arch Pathol Lab Med 119:93–96
9. Kovacs K, Horvath E, Vidal S (2001) Classification of pituitary adenomas. J Neurooncol 54:121–127
10. Lopes MB, Scheithauer BW, Schiff D (2005) Pituitary carcinoma: diagnosis and treatment. Endocrine 28:115–121
11. Gabrilove JL, Anderson PJ, Halmi NS (1986) Pituitary pro-opiomelanocortin-cell carcinoma occurring in conjunction with a glioblastoma in a patient with Cushing's disease and subsequent Nelson's syndrome. Clin Endocrinol (Oxf) 25:117–126
12. Ahmed M, Kanaan I, Alarifi A, Ba-Essa E, Saleem M, Tulbah A, McArthur P, Hessler R (2000) ACTH-producing pituitary cancer: experience at the King Faisal Specialist Hospital & Research Centre. Pituitary 3:105–112
13. Bates AS, Buckley N, Boggild MD, Bicknell EJ, Perrett CW, Broome JC, Clayton RN (1995) Clinical and genetic changes in a case of a Cushing's carcinoma. Clin Endocrinol (Oxf) 42:663–670
14. Casson IF, Walker BA, Hipkin LJ, Davis JC, Buxton PH, Jeffreys RV (1986) An intrasellar pituitary tumour producing metastases in liver, bone and lymph glands and demonstration of ACTH in the metastatic deposits. Acta Endocrinol (Copenh) 111:300–304
15. Ceyhan K, Yagmurlu B, Dogan BE, Erdogan N, Bulut S, Erekul S (2006) Cytopathologic features of pituitary carcinoma with cervical vertebral bone metastasis: a case report. Acta Cytol 50:225–230
16. Cohen H, Dibble JH (1936) Pituitary basophilism associated with a basophil carcinoma of the anterior lobe of the pituitary gland. Brain 59:395–407
17. Della CS, Corsello SM, Satta MA, Rota CA, Putignano P, Vangeli V, Colosimo C, Anile C, Barbarino A (1997) Intracranial and spinal dissemination of an ACTH secreting pituitary neoplasia. Case report and review of the literature. Ann Endocrinol (Paris) 58:503–509
18. Farrell WE, Coll AP, Clayton RN, Harris PE (2003) Corticotroph carcinoma presenting as a silent corticotroph adenoma. Pituitary 6:41–47
19. Feiring EH, Davidoff LM, Zimmerman HM (1953) Primary carcinoma of the pituitary. J Neuropathol Exp Neurol 12:205–223
20. Forbes W (1947) Carcinoma of the pituitary gland with metastases to the liver in a case of cushing's syndrome. J Pathol Bacteriol 59:137–144
21. Gaffey TA, Scheithauer BW, Lloyd RV, Burger PC, Robbins P, Fereidooni F, Horvath E, Kovacs K, Kuroki T, Young WF Jr, Sebo TJ, Riehle DL, Belzberg AJ (2002) Corticotroph carcinoma of the pituitary: a clinicopathological study. Report of four cases. J Neurosurg 96:352–360
22. Garrao AF, Sobrinho LG, Pedro O, Bugalho MJ, Boavida JM, Raposo JF, Loureiro M, Limbert E, Costa I, Antunes JL (1997) ACTH-producing carcinoma of the pituitary with haematogenic metastases. Eur J Endocrinol 137:176–180
23. Gatti G, Limone P (1984) ACTH-producing hypophyseal carcinoma monitored by computed tomography. Diagn Imaging Clin Med 53:292–297
24. Heukamp I, Ventz M, Lochs H (2004) Hypophyseal ACTH-cell carcinoma after several surgical interventions and radiotherapy. Dtsch Med Wochenschr 129:310–312
25. Hinton DR, Hahn JA, Weiss MH, Couldwell WT (1998) Loss of Rb expression in an ACTH-secreting pituitary carcinoma. Cancer Lett 126:209–214

26. Holthouse DJ, Robbins PD, Kahler R, Knuckey N, Pullan P (2001) Corticotroph pituitary carcinoma: case report and literature review. Endocr Pathol 12:329–341
27. Kaiser FE, Orth DN, Mukai K, Oppenheimer JH (1983) A pituitary parasellar tumor with extracranial metastases and high, partially suppressible levels of adrenocorticotropin and related peptides. J Clin Endocrinol Metab 57:649–653
28. Kemink SA, Wesseling P, Pieters GF, Verhofstad AA, Hermus AR, Smals AG (1999) Progression of a Nelson's adenoma to pituitary carcinoma; a case report and review of the literature. J Endocrinol Invest 22:70–75
29. Kouhara H, Tatekawa T, Koga M, Hiraga S, Arita N, Mori H, Sato B (1992) Intracranial and intraspinal dissemination of an ACTH-secreting pituitary tumor. Endocrinol Jpn 39:177–184
30. Landman RE, Horwith M, Peterson RE, Khandji AG, Wardlaw SL (2002) Long-term survival with ACTH-secreting carcinoma of the pituitary: a case report and review of the literature. J Clin Endocrinol Metab 87:3084–3089
31. Levesque H, Freger P, Gancel A, Tayot J, Courtois H (1991) Primary carcinoma of the pituitary gland with Cushing's syndrome and metastases. Apropos of a case with review of the literature. Rev Med Interne 12:209–212
32. Lormeau B, Miossec P, Sibony M, Valensi P, Attali JR (1997) Adrenocorticotropin-producing pituitary carcinoma with liver metastasis. J Endocrinol Invest 20:230–236
33. Masuda T, Akasaka Y, Ishikawa Y, Ishii T, Isshiki I, Imafuku T, Ogihara T, Miyazaki H, Asuwa N (1999) An ACTH-producing pituitary carcinoma developing Cushing's disease. Pathol Res Pract 195:183–187
34. Moore TJ, Dluhy RG, Williams GH, Cain JP (1976) Nelson's syndrome: frequency, prognosis, and effect of prior pituitary irradiation. Ann Int Med 85:731–734
35. Nawata H, Higuchi K, Ikuyama S, Kato K, Ibayashi H, Mimura K, Sueishi K, Zingami H, Imura H (1990) Corticotropin-releasing hormone- and adrenocorticotropin-producing pituitary carcinoma with metastases to the liver and lung in a patient with Cushing's disease. J Clin Endocrinol Metab 71:1068–1073
36. Nose-Alberti V, Mesquita MI, Martin LC, Kayath MJ (1998) Adrenocorticotropin-Producing Pituitary Carcinoma with Expression of c-erbB-2 and High PCNA Index: A Comparative Study with Pituitary Adenomas and Normal Pituitary Tissues. Endocr Pathol 9:53–62
37. Papotti M, Limone P, Riva C, Gatti G, Bussolati G (1984) Malignant evolution of an ACTH-producing pituitary tumor treated with intrasellar implantation of 90Y. Case report and review of the literature. Appl Pathol 2:10–21
38. Queiroz LS, Facure NO, Facure JJ, Modesto NP, Lopes DF (1975) Pituitary carcinoma with liver metastases and Cushing syndrome. Report of a case. Arch Pathol 99:32–35
39. Richter ML, Saeger W, Leifke E, Fahlbusch R, von zur MA, Schuppert F (2000) A patient with an ACTH-producing pituitary tumor with liver metastasis. Dtsch Med Wochenschr 125:52–56
40. Roncaroli F, Scheithauer BW, Young WF, Horvath E, Kovacs K, Kros JM, Al Sarraj S, Lloyd RV, Faustini-Fustini M (2003) Silent corticotroph carcinoma of the adenohypophysis: a report of five cases. Am J Surg Pathol 27:477–486
41. Salassa RM, Kearns TP, Kernohan JW, Sprague RG, Maccarty CS (1959) Pituitary tumors in patients with Cushing's syndrome. J Clin Endocrinol Metab 19:1523–1539
42. Scheithauer BW, Fereidooni F, Horvath E, Kovacs K, Robbins P, Tews D, Henry K, Pernicone P, Gaffrey TA Jr, Meyer FB, Young WF Jr, Fahlbusch R, Buchfelder M, Lloyd RV (2001) Pituitary carcinoma: an ultrastructural study of eleven cases. Ultrastruct Pathol 25:227–242
43. Sheldon WH, Golden A, Bondy PK (1954) Cushing's syndrome produced by a poultry basophil carcinoma with hepatic metastases. Am J Med 17:134–142
44. Singh G, Pais P, Garg I (2000) Refractory hypokalemia in metastatic adrenocorticotrophic hormone-secreting pituitary carcinoma. J Assoc Physicians India 48:448–449
45. Suzuki K, Morii K, Nakamura J, Kaneko S, Ukisu J, Hanyu O, Nakagawa O, Aizawa Y (2002) Adrenocorticotropin-producing pituitary carcinoma with metastasis to the liver in a patient with Cushing's disease. Endocr J 49:153–158
46. Tonner D, Belding P, Moore SA, Schlechte JA (1992) Intracranial dissemination of an ACTH secreting pituitary neoplasm–a case report and review of the literature. J Endocrinol Invest 15:387–391
47. Zafar MS, Mellinger RC, Chason JL (1984) Cushing's disease due to pituitary carcinoma. Henry Ford Hosp Med J 32:61–66
48. Zahedi A, Booth GL, Smyth HS, Farrell WE, Clayton RN, Asa SL, Ezzat S (2001) Distinct clonal composition of primary and metastatic adrencorticotrophic hormone-producing pituitary carcinoma. Clin Endocrinol (Oxf) 55:549–556
49. Newell-Price J, Trainer P, Besser M, Grossman A (1998) The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 19:647–672
50. Kars M, Roelfsema F, Romijn JA, Pereira AM (2006) Malignant prolactinoma: case report and review of the literature. Eur J Endocrinol 155:523–534
51. Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB (2005) Clinical review: diagnosis and management of pituitary carcinomas. J Clin Endocrinol Metab 90:3089–3099
52. Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF (2002) Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol (Oxf) 56:541–551
53. Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, Roelfsema F, Romijn JA (2003) Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. J Clin Endocrinol Metab 88:5858–5864
54. Hofmann BM, Fahlbusch R (2006) Treatment of Cushing's disease: a retrospective clinical study of the latest 100 cases. Front Horm Res 34:158–184
55. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? Clin Endocrinol (Oxf) 54:617–626
56. Blevins LS Jr, Christy JH, Khajavi M, Tindall GT (1998) Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J Clin Endocrinol Metab 83:63–67
57. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B (2005) Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63:549–559
58. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M (1996) Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 81:2647–2652
59. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X (2007) Corticotroph tumor progression after adrenalectomy in Cushing's disease: A reappraisal of Nelson's syndrome. J Clin Endocrinol Metab 92:172–179
60. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Patient's age is a simple predictive factor for the development of Nelson's syndrome after total adrenalectomy for Cushing's disease. J Clin Endocrinol Metab 79:887–889

61. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM (1995) The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 80:165–171

62. Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, Laws ER Jr, Young WF Jr (2000) Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 47: 723–729