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Treatment of pituitary–dependent Cushing's syndrome: long-term results of unilateral adrenalectomy followed by external pituitary irradiation compared to transsphenoidal pituitary surgery

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Summary

BACKGROUND The preferred treatment of Cushing's disease (CD) nowadays is transsphenoidal pituitary surgery (TPS). Prior to TPS, patients at the Leiden University Medical Centre were treated by unilateral adrenalectomy followed by external pituitary irradiation (UAPI). We report on long-term results of both UAPI and TPS and compare remission, relapse rates, and complications.

PATIENTS AND METHODS A retrospective study was carried out on 130 patients with CD. Patients with pituitary macroadenoma were excluded. Eighty-six and 44 patients underwent UAPI and TPS, respectively. Of these patients, 85 and 41 were evaluable for long-term results.

RESULTS Remission following UAPI and TPS was identical at 64% (54/85 and 27/41). Cumulative relapse was also comparable – 17% (9/54) and 22% (6/27), respectively, – for UAPI and TPS, although the mean follow-up periods were different – 21·4 years and 8·5 years, respectively. Cumulative disease-free survival curves after UAPI and TPS are identical until 5 years of follow-up, but diverge thereafter indicating more sustained remissions following UAPI ($P = 0{\cdot}17$, Wilcoxon statistic). Pituitary dysfunction following UAPI (36%) and pituitary surgery (55%) likewise did not differ significantly. However, pituitary dysfunction was an immediate event after TPS, whereas it developed after a mean interval of 17·8 years following UAPI.
Low-dose dexamethasone testing during follow-up had no value in predicting therapeutic outcome.

CONCLUSIONS The results of unilateral adrenalectomy followed by external pituitary irradiation do not justify that this therapy is totally abandoned in favour of transsphenoidal pituitary surgery. Unilateral adrenalectomy followed by external pituitary irradiation is a valid therapeutic modality for the treatment of Cushing's disease, and could be considered as alternative to bilateral adrenalectomy and under some circumstances to transsphenoidal pituitary surgery.

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Transsphenoidal pituitary surgery (TPS) is currently the generally accepted primary treatment of pituitary–dependent Cushing's syndrome (Cushing's disease, CD). In experienced hands the immediate results of TPS are quite satisfactory with remission in 70–94% of the patients (Bochicchio *et al*., 1995; Lüdecke *et al*., 1996) but conclusive evaluation requires a more prolonged follow-up.

In the period before TPS many centres performed bilateral adrenalectomy for CD. At the Leiden University Medical Centre (LUMC) patients with CD were treated by unilateral adrenalectomy followed by external pituitary irradiation (UAPI). The intention of the combination therapy was to correct hypercortisolism by destruction of the pituitary microadenoma, but to avoid acute adrenal insufficiency (Addisonian crises) and Nelson's syndrome as the main consequences of bilateral adrenalectomy. In an earlier report, this combination therapy was shown to cause remission in 62% of the patients. (van Seters *et al*., 1974) Therefore, UAPI remained the primary treatment in CD in our hospital until the introduction of TPS in 1978. The main goal of this study was to evaluate the long-term results of UAPI, since untoward effects of radiation therapy, such as pituitary failure, and relapse of CD may increase in time. Furthermore, we compared the results of UAPI with the outcome of TPS performed in the LUMC, to see whether UAPI could still be useful in the treatment of CD.

Patients with a pituitary macroadenoma were excluded, since in this condition adrenal surgery represents no therapeutic option.

Patients and methods

Patients

Records of 132 patients with proven CD that were treated from

1947 until 1993 at the LUMC by either UAPI or TPS were studied. Patients who received therapies prior to UAPI or TPS and two cases of ectopic ACTH-production, which became manifest only after long-term follow-up were excluded. Until 1980, 88 patients were scheduled for UAPI, but two patients died prior to pituitary irradiation. Thus, this treatment was completed in 86 patients (67 women and 19 men). One patient died within a few months after treatment. Therefore, 85 patients could be evaluated during follow-up. TPS was carried out in 44 patients (37 women and 7 men), of whom one patient died postoperatively and two patients were lost to follow-up within three months. Therefore, 41 patients remained for long-term evaluation. The mean age at therapy in the UAPI group was 34·6 ± 13·3 years (range 11–60), and 36·6 ± 15·1 years (range 12–68) in the TPS group, respectively (Table 1).

After initial treatment, outpatient follow-up visits of these 126 patients were scheduled with an interval of two months, until clinical remission. Subsequent evaluations, including laboratory tests, were performed less frequently. Follow-up lasted until the end of 1995.

Methods

Diagnosis of CD. The diagnosis of CD was based on the typical clinical features and laboratory work up.

We used the following biochemical criteria:

- increased basal urinary free cortisol (UFC) (> 220 nmol/24 h) (since 1977), 17-ketogenic steroids (17-KGS) (> 55 (women) and > 76 μmol/24 h (men)) (since 1951), and/or cortisol secretion rate (CSR) (> 78·5 μmol/24 h) (from 1962 till 1970);
- elevated basal serum levels of cortisol (>500 −> 300 −> 170 nmol/l at 0800 h – 1700 h – 2300 h) (since 1960), associated with detectable or slightly increased plasma ACTH levels (since 1975);
- insufficient reduction of serum cortisol release by low-dose dexamethasone orally (three times 1 mg daily for 5 days (17-KGS > 50% of baseline value at fifth day)) or 1 mg at 23·00 hours (cortisol > 80 nmol/l the next morning at 0800 h) (since 1970);
- adequate response of 17-KGS to high-dose dexamethasone (three times 1 mg daily for 5 days), followed by four times 2 mg daily for 2 days (17-KGS ≤ 50% of baseline value on seventh day) (since 1962);
- adequate response of 17 – KGS (> 200% of baseline value) to oral administration of metyrapone (750 mg q.i.d. for 2 days) (from 1964 till 1990);
- adequate response of serum cortisol (increase of ≥ 200 nmol/l) to 10 IE lysine vasopressin (from 1961 till 1991) or 100 μg CRF (since 1983).

Steroid hormones and metabolites in blood and urine were determined as previously described. (van Seters & Moolenaar, 1991; van Aalderen *et al*., 1992) Levels of pituitary hormones and IGF-1 were determined and dynamic tests were performed in accordance with earlier publications. (Roelfsema *et al*., 1985, 1987; Looij *et al*., 1986)

Table 1 Characteristics of patients with Cushing's disease treated by UAPI and TPS

	Unilateral adrenalectomy followed by external pituitary irradiation	Transsphenoidal pituitary surgery
Number of patients	86	44
Male/female ratio	19 : 67	7 : 37
Age (years) (mean)	34·6	36·6
(range)	(11–60)	(12–68)
Year of treatment	1947–80	1978–93
Lost to follow-up	1	3
Follow-up (years) (mean)	21·4	8·5
(range)	(1·0–40·3)	(2·2–16·2)

Additional studies

Pituitary macroadenoma, adrenal tumours or ectopic ACTH-producing tumours were excluded by plain films and tomograms, computed tomography (CT) and magnetic resonance imaging (MRI) of the sella turcica, adrenals, chest and abdomen. CT and MRI scanning were available since 1978 and 1987, respectively.

Inferior petrosal sinus sampling (IPSS) with or without CRF administration was carried out prior to TPS in 8 patients.

In all patients in whom TPS was unsuccessful and no histological evidence of a pituitary adenoma was found in the surgical specimen, the search for nonpituitary sources of ACTH-production was repeated.

Therapeutic procedures

Unilateral adrenalectomy followed by external pituitary irradiation

Unilateral adrenalectomy was carried out by a retroperitoneal approach. Left-and right-sided adrenalectomy was performed in 52 and 34 patients, respectively. External irradiation of the pituitary region was started after a median interval of one month (range 2 weeks to 2 months) following adrenalectomy, by either of two modalities: telecobalt or a linear accelerator technique, using a rotational or opposing parallel field technique with the patient being fixed with a facial mould. The median total radiation dose was 30 Gy (range 18–54 Gy) given over a period of 3–4 weeks (8–10 Gy per week), in a fractional dose of 2 Gy.

Transsphenoidal pituitary surgery

Selective TPS. The removal of all apparent abnormal or doubtful tissue, preserving at least half of the pituitary gland – was carried out in 37 patients (84%).

Radical TPS. The removal of all normal or doubtful tissue, preserving only a small rim of normal pituitary tissue (subtotal hypophysectomy) or with no visible tissue left (total hypophysectomy) – was performed in 7 patients (16%).

The choice between *selective* and *radical* TPS was made on the basis of the intraoperative ability to identify adenomatous tissue and the results of the preoperative localization techniques.

Studies in follow-up

Remission after UAPI was defined as:

- the disappearance of features of chronic cortisol excess;
- a normalized excretion of urinary steroids (UFC from 1977 on) and/or afternoon serum cortisol;
- an adequate response of serum cortisol levels (< 80 nmol/l) to low-dose dexamethasone (from 1970 on).

Following TPS an immediate postoperative glucocorticoid deficiency was an additional requirement for remission.

This study reports on a follow-up spanning up to 40 years. Since the last two criteria of remission are based on tests introduced later during follow-up, it was not possible to fulfil are three criteria of remission immediately following UAPI in the earlier treated patients. In some UAPI patients cortisol levels could only be determined much later during follow-up when clinical features of cortisol excess had already dissappeared. However, during follow-up almost all these patients fulfilled all criteria of remission. Therefore, in a few UAPI patients it would be more appropriate to use the term eucorticism rather than remission.

Relapse was defined as the reappearance of clinical and biochemical evidence of cortisol excess.

Since active CD may be associated with disturbed pituitary hormone release (Orth *et al*., 1992) pituitary integrity following UAPI and TPS was only evaluated in patients with sustained remission. Pituitary function tests were performed repeatedly during follow-up. During the long follow-up period of 40 years the criteria used have changed. Therefore, in general, pituitary function was considered intact when all of the following requirements were met:

- normal ACTH reserve to CRF or metyrapone administration;
- normal serum TSH increments to TRH and/or normal serum T_4;
- normal serum LH increments to GnRH in premenopausal women and/or normal serum testosterone in men or normal basal serum FSH in postmenopausal women.

Pituitary dysfunction was defined as a subnormal response of one or more pituitary hormones following dynamic testing, subnormal levels of the respective peripheral target hormones, or the need for replacement therapy.

Results

Unilateral adrenalectomy followed by external pituitary irradiation

Complications. Postoperative complications of adrenalectomy occurred in 17 of the 88 patients (19%), and consisted of poor wound healing ($n = 8$), intraoperative bleeding exceeding 500 ml ($n = 5$), pneumothorax and pulmonary infection ($n = 4$), shock and cardiac arrythmia ($n = 4$), deep venous thrombosis of the leg ($n = 1$). Two patients died postoperatively of shock and pulmonary embolism in 1947 and 1963.

Complications of pituitary irradiation were optical nerve damage in one patient (4 years following treatment in 1967), a radiation scar of the skull in another patient (treated in 1965) (major complications), and transient baldness in 18 patients (minor complication).

Remission and relapse. (Table 2) A total of 85 patients was available for evaluation after exclusion of one patient who died of sepsis within a few months following pituitary irradiation.

The mean follow-up was 21·4 years (range 1·0–40·3 years). Remission was attained in 54 patients (64%). The patients in remission included 32 survivors to date and 13 individuals who died without CD at a mean age of 59·6 ± 19·6 years (range 42–80), 1·0–38·4 years (mean 19·6) following treatment. Relapse occurred in 9 patients (17%) after a mean follow-up of 8·3 years (range 4·3–13·4 years). The cumulative disease-free survival curve of patients in remission following UAPI is displayed in Fig. 1.

Low-dose dexamethasone suppression was tested in all but 7 patients in remission. In those seven patients this suppression test was not yet available. Normal responses were repeatedly obtained in 35 of 38 patients with sustained remission up to 39 years (mean 18 years) following UAPI. In two of the 3 remaining patients suppressibility was lost after 7 and 27 years, respectively, despite normal UFC throughout follow-up. The last patient with an inadequate response to dexamethasone became glucocorticoid dependent after 4 years. Of the 9 patients with relapsing disease, who had all been tested, 5 patients had an adequate suppressibility 4 years or less (mean 2 years) prior to relapse.

Pituitary dysfunction. (Table 3 and Table 4) Pituitary function could be evaluated in 47 patients with a sustained remission after UAPI.

Table 2 Comparison of results of UAPI with TPS (selective, radical, and combined)

	Unilateral adrenalectomy followed by external pituitary irradiation		Transsphenoidal pituitary surgery					
			Selective		Radical		Combined	
	n/N*	(%)	*n*/N	(%)	*n*/N	(%)	*n*/N	(%)
Remission	54/85	(64)	24/34	(71)	3/7	(43)	27/41	(64)
Duration (yr) (mean)	21·4		8·8		6·9		8·5	
(range)	(1·0–40·3)		(2·2–15·3)		(4·6–10·4)		(2·2–16·2)	
Relapse	9/54	(17)	6/24	(25)	0/3	(0)	6/27	(22)
Interval (yearrs) (mean)	8·3		8·9		–		8·9	
(range)	(4·3–13·4)		(2·2–13·4)				(2·2–13·4)	

* number of patients in relation to number of patients investigated for that given quality

Nineteen patients had no biochemical evidence of pituitary dysfunction, whereas 17 patients had dysfunction of one (10 patients) or more pituitary hormones (7 patients). Nine patients required hormonal replacement therapy. In 11 patients not all pituitary functions were dynamically tested, but none of them required hormonal replacement therapy on clinical grounds.

A time scale of the various observed pituitary dysfunctions is given in Table 4. Their onset was delayed with an overall mean interval following UAPI of 17·8 years (range 6–34 years).

Twenty-eight children were born from 15 patients, including two women who delivered three children prior to the onset of LH-deficiency. The remaining patients either wanted no children or had completed their family prior to treatment.

Pituitary imaging studies. CT or MRI investigation of the pituitary gland was performed in 20 patients who were in remission 17·7 ± 6·8 years (range 5–32) after UAPI. These studies demonstrated no abnormality in 25% (5/20), and a (partial) empty sella in 75% (15/20).

Additional treatment in persisting or relapsing disease. Thirty-one patients received further treatment consisting of: pituitary irradiation ($n = 5$), subtotal or total adrenalectomy ($n = 21$), and more recently TPS ($n = 3$), bromocryptine ($n = 1$) and ketoconazole ($n = 1$). Until now, additional therapy was not given in 3 patients with low-grade disease who had no clinical but only slight biochemical signs of CD. Six patients died with active CD after a mean of 11 years (range 0·5–28 years), at a mean age of 53·7 ± 19·0 years (range 23–79), following UAPI.

Transsphenoidal pituitary surgery

Complications. Surgical complications following primary TPS occurred in 23 of the 44 patients (52%). These comprised minor complications, such as diabetes insipidus for a few days ($n = 17$) or sinusitis ($n = 2$), as well as major complications, such as intraoperative bleeding, exceeding 500 ml ($n = 9$), leakage of cerebrospinal fluid ($n = 4$), and deep vein thrombosis of the arm ($n = 1$). One patient died 3 days postoperatively of cardiac failure.

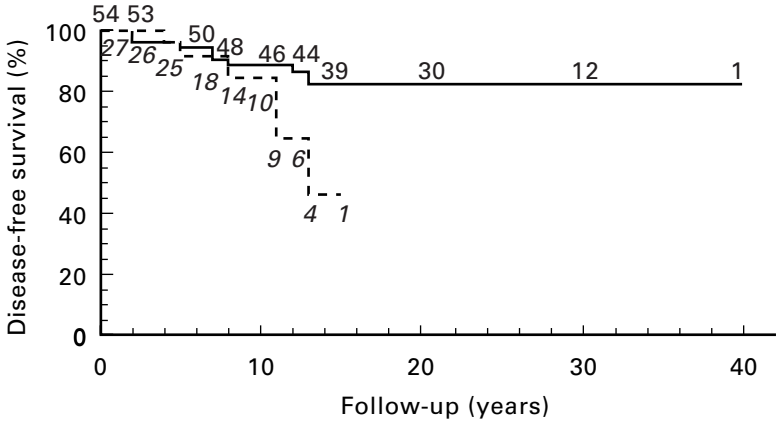

Fig. 1 Disease-free survival following successful treatment for Cushing's disease. – — Unilateral adrenalectomy followed by external pituitary irradiation (UAPI); - - - - Transsphenoidal pituitary surgery. Numbers near survival curves indicate the number of patients entering the next interval. The interval from UAPI until remission (mean 9 months) is ignored in the construction of the survival curve. We calculated the remission length from the moment patients were considered in remission (T = 0). $P = 0.17$

Table 3 Comparison of pituitary dysfunction after UAPI and TPS (selective, radical and combined) in patients in remission

	Unilateral adrenalectomy followed by external pituitary irradiation		Transsphenoidal pituitary surgery					
			Selective		Radical		Combined	
	n/N*	(%)	*n*/N	(%)	*n*/N	(%)	*n*/N	(%)
Overall dysfunction	17/47	(36)	8/18	(44)	3/3	(100)	12/22	(55)
Disturbed release of:								
FSH, LH and/or Testosterone								
All patients	8/35	(23)	8/15	(53)	2/3	(66)	10/18	(56)
Women ≤ 55 years	4/12	(33)	5/10	(50)	1/1	(100)	6/11	(55)
ACTH	13/42	(31)	4/18	(22)	3/3	(100)	7/21	(33)
TSH	4/43	(9)	0/18	(0)	2/3	(67)	2/21	(9)
IGF-1	7/12	(58)	4/11	(36)	3/3	(100)	7/14	(50)
PRL	6/37	(16)	3/12	(25)	3/3	(100)	6/15	(40)
ADH*	0/47	(0)	0/18	(0)	3/3	(100)	3/21	(14)
Need for replacement	9/47	(19)	5/18	(28)	3/3	(100)	8/21	(38)
Type of replacement								
Glucocorticoid	3		3		1		4	
Glucocorticoid + oestrogen	1		1		1		2	
Glucocorticoid + T_4	1		1		0		1	
Glucocorticoid + oestrogen + T_4	2		0		1		1	
Oestrogen + T_4	1		0		0		0	
Oestrogen	1		0		0		0	

† number of patients in relation to number of patients investigated for that given quality. * Anti-diuretic hormone; disturbed release was based on clinical grounds. The difference in occurrence of pituitary dysfunction following UAPI and TPS was statistically insignificant (chi-square test;

Table 4 Time dependency of pituitary dysfunction following UAPI for Cushing's disease

	Patients tested		Patients with pituitary dysfunction		
Function	N†	Period‡	N	Interval§	Replacement*
ACTH reserve	42	28·0 ± 9·9 (3–40)	13	19·8 ± 7·7 (12–34)	7
Reproductive					
Women ≤ 55 years	12	15·6 ± 7·6 (5–23)	4	13·5 ± 4·7 (9–18)	4
Women > 55 years	14	22·3 ± 11·1 (9–32)	6	17·0 ± 4·4 (11–22)	1
Men	9	23·6 ± 8·8 (13–38)	0	0	
All patients	35	21·4 ± 9·1 (5–38)	10	15·6 ± 4·6 (9–22)	5
Thyroid	43	22·3 ± 9·2 (6–40)	4	16·5 ± 8·3 (6–26)	4
All defects				17·8 (6–34)	

† Number of patients. ‡ Period from therapy to last test: mean ± SD (range) in years. § Interval from therapy to first detection of disturbance: mean ± SD (range) in years. * Number of patients requiring hormone replacement therapy.

Remission and relapse. (Table 2) From the group of 44 patients undergoing TPS, one patient died postoperatively. Two other patients were lost within three months of follow-up due of death (myocardial infarction) and emigration, respectively. Therefore, 41 patients remained for evaluation of *selective* (34 patients) and *radical* TPS (7 patients).

The mean follow-up was 8·5 years (range 2·2–16·2 years). Remission was attained in 24 of 34 patients (71%) and 3 of 7 patients (43%) following *selective* and *radical* TPS, respectively.

After *selective* TPS the removal of the microadenoma was confirmed in 26 patients by histological examination of the surgical specimen. Twenty-one of these patients had a remission (81%). Of the 8 patients in whose specimen no adenoma was found 3 patients had a remission (37%). In 6 of 7 patients after *radical* TPS no adenoma was found in the surgical specimen. Four of these patients were without remission.

Relapse occurred in 6 patients (25%) after a mean follow-up of 8·9 years (range 2·2–13·4 years). The cumulative disease-free survival of patients with remission after TPS is displayed in Fig. 1. The survival curve after TPS is almost identical to the curve of patients treated by UAPI for the first 5 years, thereafter the TPS curve declines more steeply than the UAPI curve.

All 24 patients, who went into remission after *selective* TPS, became glucocorticoid dependent. Dependency averaged 1·1 years (range 0·6–2·0) in 20 patients. The remaining 4 patients required glucocorticoids permanently for 3·3–16·2 years (mean 10·4 years). All patients in remission after *radical* TPS were permanently glucocorticoid dependent.

Ten of 13 patients, who were successfully treated by *selective* TPS could be repeatedly tested with low-dose dexamethasone, showing adequate responses up to $3{\cdot}9 \pm 2{\cdot}4$ years (range 0–7) prior to end of follow-up. Low-dose dexamethasone suppressibility was also normal in 5 of the 6 patients $2{\cdot}8 \pm 2{\cdot}2$ years (range 0–6) prior to relapse.

Pituitary dysfunction. (Table 3) Pituitary function after *selective* TPS was evaluated biochemically in all 18 patients in remission. In 7 patients, no biochemical evidence of pituitary dysfunction was obtained. Eight patients had evidence of single (5 patients) or multiple (3 patients) pituitary hormone dysfunction with need for hormonal replacement therapy in five. In three patients not all pituitary hormones were dynamically tested, but none of them needed hormonal replacement therapy clinically.

Four children were born from 4 patients. One female patient was treated for infertility.

All three patients in remission following *radical* TPS had multiple pituitary hormone deficiencies, including antidiuretic hormone (ADH) deficiency, and required hormonal substitution.

Additional treatment for persisting or relapsing disease. Twenty patients had persisting or relapsing CD following TPS. In 15 of these patients further treatment consisted of pituitary reoperation ($n = 4$), pituitary irradiation ($n = 6$), total adrenalectomy ($n = 2$), UAPI ($n = 1$) and treatment with ketoconazole ($n = 1$) or bromocriptine ($n = 1$). In five patients no further treatment was given because of death ($n = 1$) or low-grade disease ($n = 4$).

Pituitary reoperation. Pituitary reoperation was performed in four premenopausal female patients after *selective* TPS. Two of them had a relapse after a remission of 2·2 and 11·8 years, while the other two had persisting disease. In two patients *selective* TPS was repeated with remission in one, and two patients had successful *radical* TPS. The duration of remission in these three patients until the end of follow-up was 1·7, 2·7 and 15·7 years, respectively.

All three patients in remission had multiple pituitary hormone deficiencies (including LH, ACTH, TSH and ADH) requiring hormone replacement.

Complications following reoperation occurred in 3 of 4 patients (75%) and consisted of laryngitis ($n = 1$) (minor complication), and leakage of cerebrospinal fluid ($n = 1$), bleeding > 500 ml ($n = 1$), and subdural haematoma ($n = 1$) (major complications).

Discussion

Retrospective studies are often hard to interpret due to changes in diagnostic criteria and treatment during follow-up. This is particularly true for CD, in which pituitary irradiation and adrenal surgery were favoured as mutually exclusive therapeutic options for many years. Whereas, prior to the introduction of TPS, bilateral adrenalectomy had become the therapy of choice in most centres, our group, from 1947 to 1980, adhered to UAPI for all cases of CD without evidence of a pituitary macroadenoma. This strategy enabled us to perform a follow-up study of UAPI, as one single therapeutic modality, which embraces up to four decades, and to compare the results with those of TPS, by similar criteria. UAPI has attained little attention outside our centre except for three studies including a total of 36 patients. The results were comparable to ours with an average remission rate of 58%, during a mean follow-up period of no more than 5·8 years. (Soffer *et al*., 1961; Landau *et al*., 1978; Lamberts *et al*., 1980)

The main therapeutic goal of UAPI was to correct hypercortisolism by destruction of the pituitary microadenoma and to avoid permanent dependence on glucocorticoid substitution and the development of Nelson's syndrome as consequences of bilateral adrenalectomy. Our earlier experience with this combination therapy, showing a remission rate of

62% in 66 patients (van Seters *et al*., 1974) is now extended to follow-up periods of up to 40 years (average 21·4 years) in a series of 85 unselected patients. The initial remission rate in the present data was similar tot the previous one (64%), but late relapses occurred in 17%, after an apparent cure of 4–13 years.

There are a few data in the literature on the results of unilateral adrenalectomy alone. In our experience, only one of our seven patients treated this way had a temporary clinical improvement lasting less than 2 years. Unilateral adrenalectomy by itself reduced CSR with no more than 16% of preoperative levels. In this centre, a remission was obtained in just 20% of CD patients treated by pituitary irradiation alone using a similar dose and technique as with UAPI. According to a recent review, pituitary irradiation, with doses of 20–50 Gy, resulted in a remission rate of 40% at the most, with follow-up periods of 2–9·5 years. (Miller & Crapo, 1993) The superiority of UAPI over pituitary irradiation alone is unexplained. It could be due to increased pituitary radiosensititvity as a result of ACTH-cell activation following adrenalectomy. In rats, a transient proliferation of corticotrophes is induced by adrenalectomy. (Childs, 1987; Taniguchi *et al*., 1995) A similar superior effect of pituitary irradiation, when combined with chemical adrenal suppression using mitotane or metyrapone in patients with CD (Schteingart *et al*., 1980; Howlett *et al*., 1989) would fit with this hypothesis. A major disadvantage of these reported combination therapies is the long-term exposure of patients to the adverse effects of the adrenal suppressive agents. This is inherent to the fact that prolonged administration of these drugs is needed to induce and retain remission.

To evaluate complications of UAPI the two elements of this combined therapy should be considered separately. As to adrenalectomy, mild to severe complications, including two postoperative deaths in 1948 and 1963, occurred in 19% of the patients. This is in agreement with other reports. (Scott *et al*., 1977; Welbourn, 1985; Grabner *et al*., 1991; Favia *et al*., 1994) Nowadays, the use of laparoscopic techniques has made adrenalectomy a better tolerated procedure with fewer complications. (Prinz, 1995)

Pituitary irradiation resulted in optical nerve damage in one of our patients and a radiation scar in another, but caused no other complications. Others report less favourable experiences in their patients who, however, received a higher total or fractional dose of radiation. (Aristizabal *et al*., 1977; Grattan-Smith *et al*., 1992) The irradiation techniques have improved considerably since, resulting in less complications. (Mehta & Rozental, 1995)

Pituitary dysfunction, following pituitary irradiation and presumably of pituitary-hypothalamic origin, occurred in 36% of the cases. However, these sequelae developed after a substantial delay, as exemplified by the onset of gonadotrophin failure in two women, one to eight years after pregnancies and three uncomplicated deliveries. In no instance was fertility compromised, resulting in a total of 28 offspring (in 15 patients). All patients in the younger age group resumed satisfactory statural growth. Hormonal substitution was eventually needed in nine patients (19%), including glucocorticoids in seven cases. The incidence of pituitary failure is higher than in our earlier report with shorter follow-up (van Seters *et al*., 1974) and appears to increase with time. Whether improvements in irradiation techniques can also reduce the occurrence of pituitary dysfunction remains to be seen, since functional disturbances take considerable time to develop.

Reversal of cortisol excess after pituitary irradiation required prolonged periods of time (mean 9 months). Such delayed response to irradiation is also reported by others (Schteingart *et al*., 1980; Howlett *et al*., 1989; Tyrrell & Wilson, 1994; Estrada *et al*., 1997) and is unexplained. In the past, this delay made UAPI less suitable for severe cases of CD, but cortisol excess can now be medically controlled until definite remission is achieved. (Miller & Crapo, 1993)

Nelson's syndrome, one of the main drawbacks of total adrenalectomy, occurring in 8–80% of the patients rendered glucocorticoid dependent (for review see Nagesser *et al*. 2000) did not develop after UAPI, even after prolonged periods of glucocorticoid deficiency. On the contrary, a large number of patients in remission had a (partial) empty sella on CT or MRI.

The second part of this study concerned the evaluation of patients treated by TPS in our hospital, as related to the literature, and compares the results obtained with those of UAPI. Our remission rate of 71% after *selective* TPS is less than the 74–94% reported in literature, but the reported mean follow-up was only 2–5 years (Lüdecke *et al*., 1996) whereas our follow-up averaged 8·8 years. Moreover, in patients with a histologically verified adenoma, treated by *selective* TPS, our remission rate (81%) was more satisfactory. Except from inadequate tumour localization, failures of TPS can also result from its application in unidentified nonpituitary ACTH-excess. Among our 9 failures with negative pituitary histology, 6 patients were cured by additional pituitary irradiation, whereas an ectopic ACTH-producing source was reasonably excluded by IPSS in one patient and long-term endocrine and radiological follow-up in two others. In accordance with reports by others (Kruse *et al*., 1992) a remission was obtained in 5 of 14 patients in whom the surgical specimen disclosed no adenoma.

In our series, relapses occurred in 25%, treated by *selective* TPS, 2–13 years after a true remission. Reported relapse rates vary from 2 to 14%, but are pertained to a significantly shorter follow-up period, and are expected to increase with longer follow-up. (Lüdecke *et al*., 1996) This is also borne out by the disease-free survival curve after TPS for our patients (Fig. 1) and the curve in the normal CT-group of the European

Cushing's Disease Survey Group (ECDSG) (Bochicchio *et al*., 1995). These two curves are quite comparable until 10 years after TPS. From then on our curve declines more steeply, but such data are not given by the ECDSG, and usually are not available in the general medical literature. It is therefore fair to say that 10 years after therapy our TPS results hardly differ from those in the ECDSG's microadenoma group. Due to late relapses of 15% (our data) and 30% (ECDSG data), the respective remission rates after 10 years decreased from, respectively, 71% and 80% to 54% and 53% of the patients treated.

Surgical complications of TPS occurred in 52% of the patients and mostly involved minor complications such as transient diabetes insipidus. As to the number of major complications our data correspond to those of others. (Bochicchio *et al*., 1995) Pituitary dysfunction was encounterd in almost one half (44%) of the patients following *selective* TPS, requiring hormonal replacement therapy in 28%. These findings are comparable to some reports (Burke *et al*., 1990; Lindholm, 1992; Trainer *et al*., 1993) while others report less dysfunction (McCance *et al*., 1993; Knappe & Lüdecke, 1996; Devoe *et al*., 1997). However, we used the same strict criteria as were applied in the UAPI group to detect pituitary dysfunction following pituitary irradiation.

When we finally compare UAPI and TPS as to their therapeutic effects, TPS was superior when adenomatous tissue was properly localized, excised and confirmed histologically. Although, the disease-free survival curves of patients treated by TPS and UAPI are almost identical during the first 5 years following therapy, the two curves diverge with a trend towards more sustained remissions after UAPI. However, at the present date of follow-up this difference is not significant ($P = 0{\cdot}17$, Wilcoxon statistic).

It remains difficult to predict which patients will exhibit recurrent disease after UAPI or TPS. In our experience, low-dose dexamethasone testing during follow-up is unreliable for this purpose, since both adequate suppressibility shortly before recurrence as well as inadequate responses prior to the development of glucocorticoid dependency were found. The occurrence of relapse even after years of remission following TPS or UAPI emphasizes the need for long-term follow-up of all patients presumed cured of CD.

Permanent glucocorticoid dependence and pituitary dysfunction developed with equal frequency. However, these complications developed slowly over a number of years after UAPI, whereas they were immediate sequelae following TPS. This should be kept in mind, specifically when younger patients are involved who are at increased risk for relapse after TPS. (Bochicchio *et al*., 1995; Leinung *et al*., 1995; Knappe & Lüdecke, 1996; Devoe *et al*., 1997)

The efficacy of UAPI is probably due mainly to pituitary irradiation. However, some form of synergism is suspected because the result of pituitary irradiation in combination with unilateral adrenalectomy (our data), chemical adrenal suppression (Schteingart *et al*., 1980; Howlett *et al*., 1989), or prior pituitary operation (Estrada *et al*., 1997) is better than that of pituitary irradiation alone. (Miller & Crapo, 1993) It could be that the pituitary gland becomes more susceptible to radiation therapy as a result of the above mentioned additional therapies.

We conclude that in the past UAPI has provided a quite reasonable mode of therapy in CD and under certain circumstances should still be considered at the present time:

- as a primary therapy, in the absence of adequate neurosurgical facilities or when no pituitary adenoma can be visualized by preoperative imaging. The latter condition hampers the outcome of transsphenoidal pituitary surgery;
- as an alternative to bilateral adrenalectomy in failures of transsphenoidal pituitary surgery.

The most striking differences between transsphenoidal pituitary surgery and unilateral adrenalectomy followed by external pituitary irradiation relate to temporal aspects of their therapeutic effects. After transsphenoidal pituitary surgery both remission and endocrine complications develop at once, whereas in unilateral adrenalectomy followed by external pituitary irradiation their onset is delayed, which in case of the complications may be advantageous for patients at or before the reproductive age.

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