Nonfunctioning Pituitary Macroadenomas

Treatment and long-term follow-up

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General introduction

CHAPTER 1

I. ANATOMY AND PATHOLOGY OF THE PITUITARY GLAND

The pituitary is a small neuro-endocrine organ with a diameter of only 1 centimetre, and a weight of about 0.5 gram. It is attached to the hypothalamus by the pituitary stalk and a portal system. The pituitary is composed of two morphologic and functional different components: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The adenohypophysis consists of five different endocrine cell types, identified by antibodies against pituitary hormones and capable of production and secretion of pituitary hormones:

1. Somatotroph cells. These cells are acidophilic and produce growth hormone (GH).
2. Lactotroph cells. These cells are acidophilic and produce prolactin.
3. Corticotroph cells. These cells are basophilic and produce adenocorticotrophic hormone (ACTH), pro-opiomelanocortin (POMC), melanocyte stimulating hormone (MSH) and endorphins.
4. Thyreotrophic cells. These cells are basophilic and produce thyrotrophin (TSH).
5. Gonadotrophic cells. These cells are basophilic and produce luteinising hormone (LH) and follicle-stimulating hormone (FSH).

The neurohypophisis produces the hormones oxytocin and arginine vasopressin (AVP).

II. PITUITARY TUMORS

Different lesions may present as a mass within the sella turcica. In unselected autopsy series, the prevalence of pituitary tumors varies between 2 and 27%, with an average prevalence of 11% in a compilated series of 12.411 patients (1-3). The prevalence of adenomas > 1.0 centimetres in these series is less than 1% (1-4). Moreover, in series of CT or MR-imaging, in 10-20% of all patients small pituitary tumors can be detected (5;6). The differential diagnosis of a sellar mass is shown in Table 1 (adapted from Post *et al* (7) and Sam *et al* (8))**.** The differentiation between the various conditions causing a pituitary mass can sometimes be difficult, because these tumors may share similar clinical presentation and radiological features.

In patients operated for pituitary tumors, pituitary adenomas account for more than 90% of the tumors (9). Of other causes, the most common diagnosis is Rathke's cleft cyste (28%), craniopharyngioma (14%), metastatic carcinoma (12%), chordoma (11%) and meningioma (10%) (9). The proportion of patients with functioning, respectively, nonfunctioning adenomas among patients with pituitary adenomas, is dependent on the applied selection criteria. In series of patients operated for pituitary tumors, 25-50% of the adenomas is nonfunctioning, 50-75% is functioning. Off all pituitary adenomas, 40%-50% is clinical nonfunctioning (3;10;11). In autopsy series, the vast majority being

Table 1. Differential diagnosis of sellar masses

Differential diagnosis of sellar masses
I Pituitary adenomas
Nonfunctioning adenomas
Functioning adenomas
Prolactinomas
Cushing's disease
Acromegaly
Thyreotroph adenomas
Gonadotroph adenomas
II Cystic lesions
Rathke's cleft cyste
Craniopharyngioma
Arachnoid cyst
III Neoplasms
Meningioma
Germ cell tumor
Chordoma
Granular cell tumor
Glioma
Metastatic lesions
Lymphoma
IV Inflammatory/infectious lesions
Sarcoidosis
Tuberculosis
Langerhans histiocytosis
Lymphocytic hypophysitis
Pituitary abcess
V Vascular lesions
Aneurysm

microadenomas, pituitary lesions turn out to be nonfunctioning adenomas in about 50%, the other 50% mainly being hormonal active adenomas (1;12). In contrast to microadenomas, in patients with macroadenomas there is no equal distribution between functioning and nonfunctioning adenomas, nonfunctioning adenomas accounting for over 80% of all pituitary tumors (13-16). The reason for this higher prevalence of nonfunctioning pituitary adenomas is given by the fact that functioning adenomas are characterized by hormone excess, giving rise to clinical symptoms in an earlier phase of tumor growth and development.

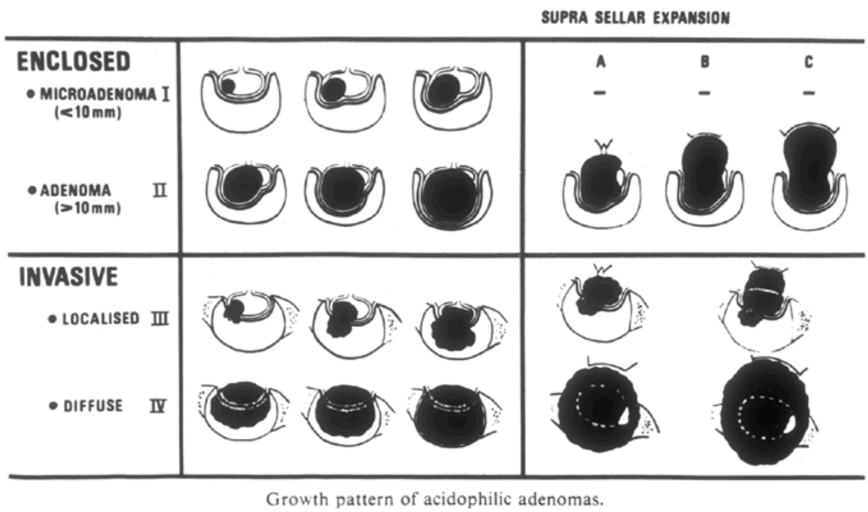
III. NONFUNCTIONING PITUITARY ADENOMAS

Pituitary adenomas

Pituitary adenomas are non-metastasing neoplasms of the pituitary, composed of adenohypophysal cells and lacking a true capsule (17;18). Pituitary adenomas are classified according to tumor size and to functionality. An adenoma with a diameter < 1 cm is defined as a microadenoma, an adenoma with a diameter > 1 cm as a macroadenoma. This differentiation between micro- and macroadenomas is clinically relevant, because, in contrast to microadenomas, macroadenomas may result in pituitary deficiencies and visual field defects. Pituitary tumors are staged according to the classification by Hardy and modified by Wilson (19). This classification is based on tumor diameter and local invasiveness (I-IV), and suprasellar/parasellar extension (A-E) (Figure 1).

Pituitary adenomas can be classified as either functioning or nonfunctioning according to their hormonal activity in vivo. Functioning adenomas are characterized by the overproduction of one, or in rare cases multiple, pituitary hormones. The hormonal activity of pituitary adenomas is usually a reflection of the underlying cytodifferentiation, which may consist of any of the cell types of the adenohypophysis. Nonfunctioning pituitary tumors are characterized by the absence of clinical and biochemical evidence of pituitary hormonal overproduction in vivo. Although from a clinical perspective nonfunctioning adenomas form a homogeneous group, from a pathological perspective they represent a heterogeneous group. By immunohistochemistry, the adenoma can be shown to consist of somatotroph, thyreotroph, lactotroph, gonadotroph or corticotroph cells, whereas adenomas also may contain multiple hormonal cells (20). Because nonfunctioning adenomas

Figure 1. Hardy-Wilson classification of pituitary tumors



lack clinical effects of hormone excess by definition, clinical nonfunctioning adenomas containing hormone producing cells are also referred to as silent pituitary adenomas. The most common silent adenomas are gonadotroph adenomas (20-22). These tumors contain immunoreactivity for α-subunits as well as β-subunits of LH and/or FSH. Adenomas that can not be classified according to immunohistochemistry are called null-cell adenomas. However, there is evidence that most cases of null-cell adenomas are gonadotroph adenomas with low expression of immunoreactivity of gonadotroph cells (21;23). Some null-cell adenomas may be composed of pluripotental progenitor cells, capable of differentiating to different hormone-producing cell lines (24).

The rare pituitary adenomas that do metastasize are mainly functional in origin (21). A malign course in nonfunctioning pituitary adenomas is extremely rare (25), although local invasion is a frequent observed phenomenon in clinically nonfunctioning adenomas (26-28).

Pathophysiology

Two different theories have been proposed to explain pituitary tumor-genesis. The first theory indicates hormonal stimulation as the initial event causing pituitary tumorgenesis. The second theory indicates an intrinsic pituitary defect as the initiating event.

Almost all pituitary adenomas, both functioning and nonfunctioning, are monoclonal in origin (3;29), whereas polyclonal pituitary adenomas are extremely rare (18). In normal female tissue one of two x-chromosomes is inactivated. This event occurs randomly, leading to polyclonality in normal tissue (3). In female patients with pituitary adenomas, monoclonality of the tumor was proven by the loss of heterozygosity in tumor tissue (29). This finding implies molecular alteration(s) as the underlying event for tumorgenesis and that pituitary adenomas arise from clonal expansion of a single mutated pituitary cell. Because of the monoclonality of the tumor, hypothalamus disorders, such as the overproduction of hypothalamic, proliferative hormones, do not seem to play an important initial pathophysiologic role in pituitary adenomas. This is established by the lack of associated hyperplasia in pituitary tissue surrounding pituitary tumors (17;18). However, although a genetic modification seems to be the initiating step, hormones and/or growth factors may play a role in promoting subsequent cell proliferation. The molecular events leading to adenoma formation are incompletely understood (30). Molecular studies have revealed that most of the mutations present in other malignancies, are usually absent in clinical nonfunctioning adenomas (18). Several genes and molecular mechanisms have been proposed to be involved. Deletions in the region 13q14 have been identified in pituitary adenomas, pointing towards a possible tumor suppressor gene at this locus (18). Loss of expression of p16 is probably involved in the pathogenesis of adenomas, particularly in null cell adenomas (31). Pituitary tumor transforming gene (PTTG) is found to be overexpressed in a wide range of pituitary adenomas, although its role in tumorgenesis is unclear (3). However, at present, the relationship between these molecular changes and clinical phenotype is unclear.

Clinical presentation

The initial presentation of nonfunctioning pituitary adenomas depends largely on size and growth pattern of the tumor. In general, nonfunctioning microadenomas do not cause symptoms, because the tumor does not exceed the anatomical borders of the sella turcica, and pituitary function is preserved. However, even in about 15-20% of all patients with nonfunctioning macroadenomas, the tumor is discovered accidentally and not accompanied by clinical symptoms (32;33). The main presenting symptoms of nonfunctioning pituitary macroadenomas are headache, visual field defects and hypopituitarism due to mass effects of the tumor. Headache is present in about 40-50% of all patients (32;33) and can be caused by increased intracranial pressure and stretch of the dura mater (18). Visual disturbances are caused by compression of the optic chiasm. Typically, macroadenomas cause bitemporal field defects, explained by the anatomy of the visual pathways in the chiasm: the crossing inferonasal nerve fibres lie at the anterior part of the chiasm and are therefore compressed first. This causes the paradigmatic pattern of visual field defects: bitemporal defects of the upper quadrant. However, depending on the growth pattern of the tumor, there may exist asymmetry between the visual field defects of the two eyes. Visual field defects are present in the vast majority of all patients presenting with a pituitary macroadenoma (32;33).

Hypopituitarism is caused by three mechanisms: 1. compression of the pituitary stalk, which causes decreased availability of hypothalamic stimulatory hormones, 2. compression of functioning pituitary tissue, and 3. hypothalamic involvement of the pituitary tumor. In the majority of patients presenting with complaints of nonfunctioning pituitary macroadenomas, pituitary insufficiency is present to some degree (34-36). In addition to pituitary deficiencies, nonfunctioning macroadenomas can be accompanied by hyperprolactinemia. The secretion and release of prolactin is inhibited by hypothalamic dopamine-release. Pituitary tumors may disrupt dopamine release by compression of the pituitary stalk, and may therefore be accompanied by modest hyperprolactinemia. A prolactin level less than 100 µg/L is compatible with compression of the pituitary stalk (37;38).

Other presenting signs of pituitary macroadenomas, though occurring infrequently, are cranial nerve dysfunction, diplopia and apoplexy. Cranial nerve dysfunction can be caused by infiltrating pituitary tumors. Apoplexy is a clinical syndrome resulting from acute haemorrhage or infarction of the pituitary tumor (39). In unselected patients with nonfunctioning macroadenomas, apoplexy is the presenting sign in about 10-25% of the patients (33;40).

Treatment

The treatment of choice for pituitary adenomas complicated by visual field defects is transsphenoidal surgery. Visual recovery has been demonstrated in the first days after surgical treatment (41;42) and is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual field defects and visual acuity improve in more than 80% of the patients after transsphenoidal surgery (33;43-45), although visual field defects and visual acuity may worsen in a limited number of patients after surgery (46-49).

The results of transsphenoidal surgery on pituitary function vary between different studies. Some studies report, to a variable degree, an improvement in pituitary function (45;50-53), whereas other studies could not demonstrate significant improvement in pituitary function (34;36;43) or even reported a decrease in pituitary function (35;54). Therefore, the aim of transsphenoidal surgery should be improvement of visual field defects, rather than improvement of pituitary function.

During long-term follow-up after transsphenoidal surgery, tumor recurrence is observed in 12-46% of the patients (43;44;55;56). The role of postoperative radiotherapy, in order to prevent tumor recurrence, is still under debate. Some centers provide postoperative radiotherapy in a selection of the patients to prevent tumor regrowth (35;36;56;57). Nonetheless, even after postoperative radiotherapy, tumor recurrence was reported in 2-36% of the irradiated patients (36;44;55;56). The possible benefit of postoperative radiotherapy, *i.e.* a decrease in long-term growth rate of pituitary adenomas, has to be balanced against potential side effects of radiotherapy such as hypopituitarism (58-60) and secondary brain tumors (61).

Mortality

Pituitary adenomas are accompanied by considerable morbidity. In macroadenomas morbidity is caused by mass effects of the tumor leading to visual field defects, decreased visual acuity and pituitary insufficiency in the majority of patients (32;33). In acromegaly and Cushing's disease, morbidity is caused by hormonal overproduction, in addition to tumor mass effect in cases of macroadenomas. In Cushing's disease, cortisol excess causes central obesity, insulin resistance, hypertension and osteoporosis (62). Moreover, cortisol overproduction is associated with increased cardiovascular risk, continuing even after remission of the disease (63). In acromegaly exposure to growth hormone excess is associated with pathological conditions such as hypertension, cardial hypertrophy, diastolic dysfunction, insulin resistance, sleep apnea and ventilatory dysfunction (64;65). In patients with functioning pituitary adenomas (66;67), nonfunctioning pituitary adenomas (68) as well as craniopharyngiomas (69), an increased standardized mortality ratio (SMR) have been reported. Moreover, in several studies, an increased SMR in patients with hypopituitarism has been reported (68;70-72). In the majority of studies the general population was used as control group to assess mortality in patients with pituitary adenomas. However, it is presently unknown to what extent the excess mortality is caused by pituitary tumors and their treatment in general, and to what extent (previous) by previous overexposure to cortisol or growth hormone.

Quality of life assessment

The assessment of Quality of Life (QoL) has increasingly become an important tool to assess the effects of disease and outcome of medical treatment. Quality of life refers to the patient's perception of their physical, mental and social health. For numerous diseases and treatment modalities quality of life has been investigated (73-80). In general, pituitary diseases are associated with impaired QoL (81). This can be explained by several factors. Macroadenomas are associated with different degrees of hypopituitarism, which require hormonal substitution. However, despite optimal endocrine replacement strategies, normal endocrine function can not be perfectly restored by exogenous substitution. It is likely that this contributes to impaired QoL parameters in hypopituitarism. Moreover, growth hormone and ACTH producing adenomas induce irreversible effects through the syndromes of acromegaly (82) and Cushing's disease (83), which persist despite long-term cure of the disease. Finally, radiotherapy for pituitary tumors is associated with decreased QoL (82).

IV. SCOPE OF THIS THESIS

In this thesis, the following important clinical aspects of the treatment of nonfunctioning pituitary macroadenomas will be addressed:

- The natural course of nonfunctioning pituitary macroadenoma
- Long-term outcome after transsphenoidal surgery
- Pattern of improvement in visual acuity after transsphenoidal surgery
- Mortality in patients with pituitary adenomas
- Quality of Life assessment

The natural course of nonfunctioning pituitary macroadenoma

Because the majority of patients with NFMA are operated, the natural course of NFMA is largely unknown. In **chapter 2** we present the outcome of a study, designed to estimate the natural course of NFMA in non-operated patients. Studies on the natural course of nonfunctioning macroadenomas are important, not only because they fill a gap in common knowledge. Until now, the majority of patients with a nonfunctioning macroadenoma will be operated in most centers, even in the absence of visual field defects (84). However, more detailed knowledge of the natural course of nonfunctioning pituitary macroadenomas may select patients in whom a conservative approach is more appropriate.

Long-term outcome after transsphenoidal surgery

Transsphenoidal surgery is the golden standard in the treatment of nonfunctioning pituitary macroadenomas with visual field defects. However, the role of postoperative radiotherapy is still under debate. Prospective trials evaluating the effect of postoperative radiotherapy on regrowth rates of NFMA have not been published. Only 2 studies have been published in consecutive NFMA patients with a wait and see policy after transsphenoidal surgery (32;43). However, these reports do not propose a wait-and-see policy for all NFMA patients.

In **chapter 3** we present the results of a treatment strategy in which postoperative radiotherapy was not applied in consecutive patients after transsphenoidal surgery. The main question was whether a treatment strategy without postoperative radiotherapy may lead to good tumor control, without adversely affecting patient's outcome. A wait-and-see policy after transsphenoidal surgery would have the advantage to postpone the possible side effects of radiotherapy in patients with tumor recurrence for several years.

Pattern of improvement in visual acuity after transsphenoidal surgery

One of the main goals of surgical treatment in nonfunctioning macroadenomas, is the restoration of visual function. The process of recovery of visual field defects starts immediately after surgery and can already be documented on the second postoperative day (41). This process of recovery is probably due to restoration of the velocity of conduction in the optic nerves. However, improvement of visual field defects appears to continue even years after initial surgical treatment (42;85). This second, slow phase of recovery may reflect restoration of axonal transport and remyelination.

The process of gradual visual improvement, has only been studied for visual field defects, not for visual acuity (42). In **chapter 4** we present data on the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

Mortality in patients with pituitary adenomas

An increased SMR has been reported in both hypopituitarism and pituitary tumors (68). However, it is presently unknown to what extent the excess mortality is caused by pituitary tumors and their treatment in general, and to what extent by (previous) exposure to cortisol or growth hormone overproduction.

In **chapter 5** we describe a single centre study to assess mortality ratios during long term follow up after transsphenoidal surgery in patients with nonfunctioning pituitary macroadenomas and Cushing's disease. To answer to the question to which extent previous exposure to hormonal overproduction *per se* is associated with increased mortality, we compared mortality in patients operated for Cushing's disease to mortality in patients operated for nonfunctioning pituitary macroadenomas.

Quality of Life assessment

Although quality of life has been investigated in patients with functioning pituitary tumors (83;86), no studies on QoL in patients treated for nonfunctioning adenomas, compared to healthy controls, have been published. Most studies on QoL in pituitary diseases were not focussed on nonfunctioning tumors, but included heterogeneous groups, consisting of both functioning and nonfunctioning pituitary tumors (87-90). In **chapter 6** we present the results of a quality of life assessment in adult patients treated by transsphenoidal surgery for nonfunctioning macroadenomas. In **chapter 7** we present the same assessment in adult patients treated for craniopharyngioma.

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The natural course of nonfunctioning pituitary macroadenomas in non-operated patients

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CHAPTER 2

SUMMARY

Objective. The natural history of nonfunctioning pituitary macroadenomas (NFMA) has not been fully elucidated. Therefore, we evaluated pituitary function, visual fields and tumor size during long-term follow-up of non-operated patients with NFMA.

Design. Follow-up study

Patients. Twenty-eight patients (age 55 ± 3 years) with NFMA, not operated after initial diagnosis, were included.

Results. Initial presentation was pituitary insufficiency in 44%, visual field defects in 14%, apoplexy in 14%, and chronic headache in 7% of the patients. The duration of follow-up was 85 ± 13 months. Radiological evidence of tumor growth was observed in 14 of 28 patients (50%) after duration of follow-up of 118 ± 24 months. Six patients (21%) were operated, because tumor growth was accompanied by visual field defects. Visual impairments improved in all cases after transsphenoidal surgery. Spontaneous reduction in tumor volume was observed in 8 patients (29%). No independent predictors for increase or decrease in tumor volume could be found by regression analysis.

Conclusion. Observation alone is a safe alternative for transsphenoidal surgery in selected NFMA patients, without the risk of irreversibly compromising visual function.

INTRODUCTION

Nonfunctioning pituitary macroadenomas (NFMA) are the most prevalent pituitary macroadenomas (1,2). Although NFMA's are benign in origin, mass effects may lead to serious clinical symptoms such as visual impairments, chronic headache and pituitary insufficiency. At the time of initial diagnosis, visual field defects are detected in 60-80% of NFMA patients (3-5). Transsphenoidal surgery is the treatment of choice in NFMA patients with visual field defects. The main aim of surgical treatment is improvement of visual function, which is achieved in over 80% of cases (3,6). Studies on the effect of surgery in NFMA on pituitary function show conflicting results. Some studies report, to a variable degree, an improvement in pituitary function (4,7-11), whereas others could not demonstrate significant improvement in pituitary function, or even showed decreased pituitary function after transsphenoidal surgery (3,5,12,13). Transsphenoidal surgery leads to long-term tumor control in ~ 80% of patients (3,14-16), and, in selected series, in even more than 90% of the patients (15,17).

The natural course of NFMA is largely unknown, because the majority of patients with NFMA are operated. The natural course of pituitary incidentalomas was reported in 5 previous reports (1,18-21). In 4 of these reports, data on the natural course of NFMA were reported (1,18,19,21). The fifth study described the combined data of both nonfunctioning microadenomas and macroadenomas, not permitting a conclusion with respect to the natural course of NFMA *per se* (20). Those studies, with a follow-up period ranging from 22 to 73 months, show an increase in tumor size ranging from 25 to 50% of all patients with NFMA. The natural course of NFMA presenting for other reasons than the presence of an incidentaloma is unclear.

The main indication for surgery in patients with NFMA in our hospital is the presence of visual impairment. In the absence of visual field defects, the initial therapeutic approach is to evaluate tumor growth and visual function with regular intervals. In patients with only minimal visual field defects surgery is deferred. The aim of the present study was to evaluate changes in pituitary function, visual function and tumor size during long-term follow-up of these non-operated patients with NFMA.

PATIENTS AND METHODS

Between 1981 and 2005, 232 consecutive patients were diagnosed with NFMA at the Leiden University Medical Center. Patients were included in this study based on the following criteria:

1. Macroadenoma on MR imaging
2. Absence of any clinical and biochemical signs of hormone-excess

3. A prolactin level below 100 µg/L to exclude possible prolactinomas (22,23)
4. Expectative approach after initial diagnosis
5. At least two sequential MRI's to evaluate tumor-growth.

The vast majority of the patients (n=195), was operated after diagnosis. In 37 patients initially an expectative approach was undertaken after diagnosis. Nine of these patients were not eligible for the present study, for the following reasons: follow-up by CT scan only (n=5), lost to follow-up (n=1), no follow-up by MRI because of very high age and the absence of visual field defects (n=2), follow-up period shorter than one year (n=1). Consequently, a total of 28 patients was included in this study. The duration of follow-up was defined as the interval between the first and the last MRI-scan. Because the study was designed to assess the natural course of NFMA's, in case of an operation for NFMA, the last MRI before surgery was assigned as the end of follow-up.

An experienced endocrinologist saw each patient, at least twice a year. Growth hormone (GH) deficiency was defined as an IGF-1 level below the reference range for age and sex (24), and/or an insufficient rise in GH levels (absolute value < 3 µg/L) after stimulation during an insulin tolerance test (ITT). Before 1992, serum GH was measured by RIA (Biolab/serono, Coinsins, Switzerland). The RIA was calibrated against WHO-IRP 66/21, with an interassay variation coefficient below 5%. From 1993 onwards GH was measured by immunofluorometric assay (Wallac, Turku, Finland), calibrated against WHO-IRP 80-505, with an interassay variation coefficient of 1.6-8.4% between 0.1 and 15 µg/L. IGF-1 determination was performed by RIA available since 1985 (INCSTAR Corp., Stillwater, MN), with an interassay variation less than 11%. ACTH deficiency was defined as a basal cortisol level at 8.00 A.M. of < 0.12 µmol/l and/or an insufficient increase in cortisol levels (absolute value < 0.55 µmol/ l) after an insulin tolerance test (ITT: nadir glucose < 2.2 nmol/L). In two patients, an ITT was contraindicated and a corticotrophin releasing hormone (CRH) stimulation test was performed, using human CRH, in which we used the same cut-off levels for cortisol concentrations like in the ITT. Cortisol was measured with three different immunoassays over time. Until 1986 cortisol was measured by in house RIA with an interassay coefficient of variation of 10%. Between 1986 and 1994 a fluorescence energy-transfer immunoassay Syva Advance (Syva Company, Palo Alto, CA) was used, with an interassay variation coefficient of 3.6 to 6.1%. From 1994 cortisol was measured by fluorescence polarisation assay on a TDx (Abbott, Abbott Park, Ill). The interassay variation coefficient is 5-6% above 0.5 µmol/l and amounts to 12% under 0.20 µmol/l. In addition, the biannual evaluation consisted of measurement of free $T_{4,}$ LH/FSH (all patients), estradiol (premenopausal female patients), and testosterone (male patients) concentrations. Prolactin was measured with a sensitive time-resolved fluoro-immunoassay (Wallac, Turku, Finland), calibrated against WHO 3rd International Standard for Prolactin 84/500. The interassay coefficient of variation was 3.4 to 6.2% in the assay range from 3.0 to 80 µg/L.

The evaluation of visual function was done by an ophthalmologist, and included visual acuity, pupillary fundus and visual fields. Visual fields were assessed by Humphrey perimetry in all patients. Goldman perimetry was used as an additional tool to assess peripheral visual field defects. Ophtalmologic assessment was performed at baseline, after six months and subsequently at yearly intervals. Visual field defects were classified as minimal if there was a small defect in only one eye in only one quadrant.

Repeat MRI was performed within one year after the initial diagnosis. If no growth was observed, subsequent MRI scanning was performed every second year.

The follow-up of the patients was part of regular medical care. The approaches described in this paper did not involve any randomization or any experimental intervention. According to Dutch law, each patient has to be fully informed on the pros and contras of each treatment strategy, and each patient can only be treated after giving oral informed consent.

Assessment of radiological imaging

Two observers evaluated all MRI scans, independently of each other. Tumor volume was assessed by measuring the largest diameter of the tumor in three directions. The vertical diameter (V) was measured on sagittal T1 weighted and coronal T1 weighted scans, anteroposterior (AP) diameter on coronal T1 weighted scans and transversal diameter (T) on T1 weighed sagittal scans.

Imaging was performed on MR scanners with different field strengths, ranging from 0.5 Tesla to 1.5 Tesla. Imaging parameters included the following: A field of view (FOV) of 190 mm^2 and a matrix size of 256 x 512 mm, yielding an in-plane spatial resolution of 0.74 x 0.37 mm (scan duration was increased at lower field strengths in order to maintain sufficient resolution). Tumor volume assessment was not performed by the same MRI-scanner in each patient, because the higher strength MRI's were not available during the initial part of the observation period of the present study.

Tumor growth was defined as an increase in tumor size on MRI of more than one millimeter in any direction, independent of the development of visual field defects. Tumor volume was assessed as the volume of a rotating ellipsoid, with the following formula: $\pi/6$ (VxAPxT) (25).

Statistics

Binary logistic regression was performed to assess predictors for increase or decrease in tumor growth. All data are expressed as mean ± standard error, unless otherwise mentioned. A p-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics (Table 1)

Twenty-eight patients were included. Mean age at presentation was 55 ± 3.3 years. The duration of follow-up was 85 months ± 13 months. Initial presentations were pituitary insufficiency in 44%, visual field defects in 14%, apoplexy in 14%, and chronic headache in 7% of the patients. In only 6 patients (21%) the macroadenoma was an incidental finding. Radiological imaging revealed a macroadenoma in all cases, with suprasellar extension in 61% and/or lateral/infrasellar extension in 44% of cases. A large number of patients had pituitary insufficiency (71%) of one (32%) or more axis (39%).

Visual field defects were present in 13 patients at initial presentation. In 6 of these patients the defects were classified as minimal. Visual acuity was normal in 6 of 7 patients with more than minimal visual field defects.

Table 1. Patient characteristics at initial presentation (n = 28)

Male/Female	15/13
Age at diagnosis (years)	55 ± 3.3
Initial Presentation	
Pituitary deficiency	44%
Incidentaloma	21%
Visual field defects	14%
Headache	7%
Apoplexia	14%
Pituitary function	
Intact function of anterior pituitary gland	29%
Single pituitary deficiency	32%
Multiple pituitary deficiencies	25%
Panhypopituitarism	14%
Prolactin (µg/L) in male patients (median + range)	13, range 0.3-50.6
Prolactin (µg/L) in female patients (median + range)	16, range -4.2 to 1.17
IGF-1 SD score (median + range)	-0.5, range -4.2 to 1.2
MRI characteristics	
Tumor volume (mm^3)	3746 ± 727
Suprasellar extension	61%
Lateral/infrasellar extension	44%
Visual field evaluation	
No visual field defects	54%
Minimal visual field defects	21%
Bitemporal visual field defects	25%

Treatment strategy

Fifteen of the 28 patients where not operated because they did not have any visual field defects. In 6 other patients a conservative approach was chosen, because they had only minimal visual field defects. Seven patients were not operated despite visual field defects for the following reasons. The pattern of the visual field defects was not compatible with the diagnosis of chiasm compression, and there was a more likely ophthalmologic explanation of the defects (N=2). In 2 other patients, one of which had decreased visual acuity, surgical treatment was contraindicated because of high age, and serious co-morbidity. Finally, in 3 patients with visual field defects and pituitary apoplexy an initial expectative approach was chosen. In all subjects a wait-and-see approach was chosen with careful follow-up of the visual function.

Radiological follow-up

All 28 patients had at least two MRI scans, with a mean interval between the first and the last MRI of 85 ± 13 months. Radiological evidence of tumor growth was observed in 14 of 28 patients (50%), after a duration of follow-up of 118 ± 24 months (Table 2). In these patients, the mean tumor volume increased from 3489 mm^3 ± 538 mm^3 to 5318 mm^3 ± 820 mm^3. The mean increase in tumor size, estimated by the growth in the diameter with the largest growth, was 0.6 mm/year. Growth velocity, expressed in mm^3, was 236 mm^3/year. If we exclude the 4 patients with apoplexy at initial presentation, because in

Table 2. Characteristics of patients with tumor enlargement (n=14)

Age at diagnosis	Female/male	Follow-up (months)	Tumor volume at diagnosis (mm^3)	Tumor volume end follow-up (mm^3)
40	F	30	3050	3577
35	F	36	1406	1631
29	F	48	2276	4382
77	F	81	1422	2454
66	F	144	4351	4853
40	F	240	5292	6351
41	M	24	761	1435
42	M	24	2197	2504
53	M	36	4445	6975
75	M	60	6778	8420
74	M	72	4710	6463
72	M	180	6328	10525
64	M	204	4832	10826
58	M	264	1004	4059
55 ± 4.4		118 ± 24	3489 ± 538	5318 ± 820

these cases subsequent tumor enlargement is less probable, an increase in tumor volume was observed in 58% of the remaining patients during prolonged follow-up.

Remarkably, reduction in tumor volume was observed in 8 patients (29%). In those 8 patients tumor volume decreased from 3040 mm^3 ± 912 mm^3 to 1434 mm^3 ± 443 mm^3. Two of those 8 patients initially presented with pituitary apoplexy.

In the remaining 6 patients (mean tumor volume 5286 mm^3 ± 3061 mm^3) no change in tumor volume could be detected by MRI. In one patient, despite a follow-up period of 216 months, no tumor growth could be observed.

Binary logistic regression was performed in a model including increase and decrease in tumor volume as dependent variable and age, gender, tumor volume, tumor extension, hypopituitarism, prolactin levels and follow-up duration as independent variables. No independent predictors for increase or decrease in tumor volume could be found by regression analysis.

Ophthalmologic follow-up

In 9 of the 14 patients, tumor growth on MRI was associated with increased defects of visual fields. In 7 of those 9 patients the visual field defects were likely caused by tumor mass effect. In the two other patients, one with glaucoma and one with uveitis, the predominant defects were not in the upper temporal quadrant. In 4 patients with tumor growth no visual field defects could be detected. In one patient, who had only minimal visual field defects, there was no increase in visual field defects. In 2 of the 8 patients with a decrease in tumor volume on MRI, an improvement of visual defects could be observed.

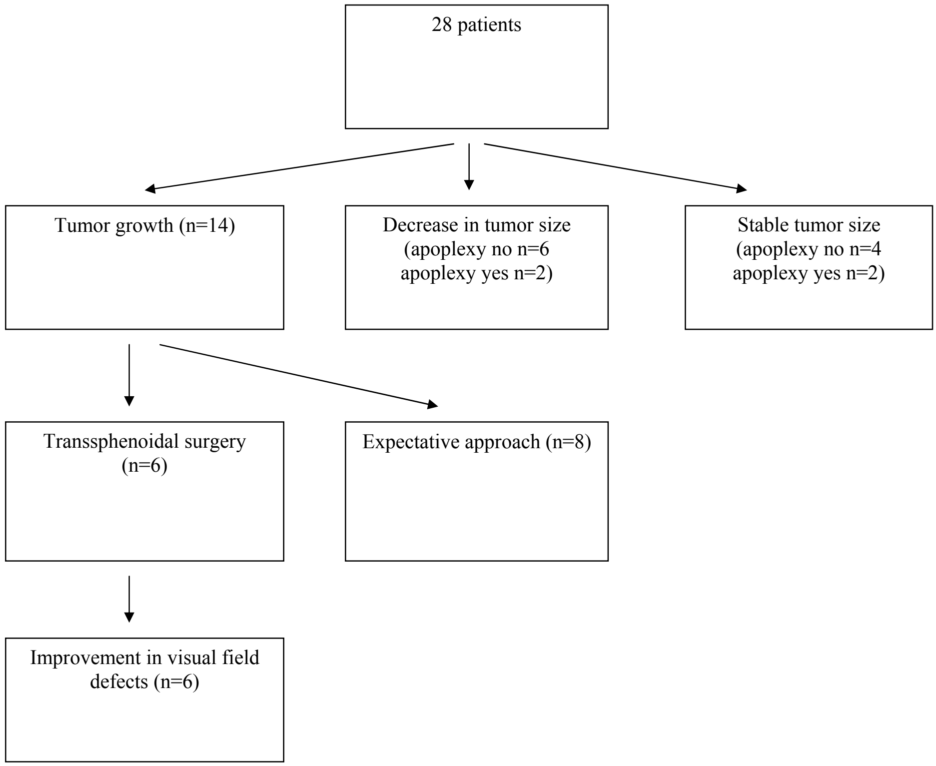
Four patients had apoplexy as presenting symptom, accompanied by visual field defects in 3 of them. In all these three patients visual fields normalized spontaneously within three months.

Endocrine follow-up

In 3 of the 14 patients with growing tumors on MRI, an increase in pituitary deficiencies was observed, whereas in the other 11 patients pituitary functions remained stable. In only one of the 8 patients with a decrease in tumor size, there was an improvement of pituitary function.

In 1 of the 4 patients with pituitary apoplexy, initial pituitary deficiencies were present in 3 of 4 axis, including ACTH deficiency. In this patient pituitary deficiencies resolved within three months. The other 3 patients presented with apoplexy had normal pituitary function

Figure 1. Long-term outcome after expectative approach for NFMA



Long-term outcome (Figure 1)

The mean follow-up period was 85 ± 13 months. At the end of follow-up, in 14 patients without signs of tumor growth on MRI, there was still no indication for surgery. Six patients were operated, because tumor growth was accompanied by visual field defects. After transsphenoidal surgery, visual field defects improved in these 6 patients. In 5 other patients with tumor growth, the conservative approach was continued because of normal visual fields (n=4), or, stable, minimal visual field defects (n=1). Three patients with tumor growth and visual field defects were not operated, because of non-compatibility of the defects with compression of the optic chiasm by NFMA (n=2), or high age and associated co-morbidity (n=1). In the last patient visual field defects were accompanied by a slight decrease in visual acuity.

DISCUSSION

In this study we evaluated the natural course of NFMA. In 28 NFMA patients, with a mean follow-up period of more than 7 years, tumor growth was observed in 14 patients (50%).

Table 3. The natural course of tumor volume in nonfunctioning pituitary macroadenomas

Author	Macroadenoma	Mean follow-up	Increase in tumor volume	Decrease in tumor volume
Feldkamp *et al.* (1)	N = 19	32 months	N = 5	N = 1
Donovan *et al.* (18)	N = 16	73 months	N = 4	N = 0
Reincke *et al.* (19)	N = 7	22 months	N = 2	N = 0
Sanno *et al.* (20)	N = 115 [a]	51 months	N = 23	N = 11
Arita *et al.* (21)	N = 42	62 months	N = 21	N = 1
Present series	N = 28	85 months	N = 14	N = 8

[a] Consisting of both nonfunctioning pituitary microadenomas and macroadenomas

In 7 of these patients, tumor growth was accompanied by (increased) visual field defects, likely to be caused by mass effects of the tumor. Surgical intervention was performed in only 21% (n=6) of all patients, and improved visual fields in all cases. Remarkably, a spontaneous decrease in tumor volume was observed in 29% of the patients during long-term follow-up. Thus, in the absence of visual impairments, observation alone is a safe alternative for surgery in selected patients with NFMA, since surgery can ultimately be withheld in the majority of these patients, without compromising visual field defects.

To date, only 4 studies reported the natural course of NFMA, discovered as incidentalomas, comprising a total of 41 patients (1,18,19,21), whereas an additional study reported the natural course of a combined series of both nonfunctioning micro- and macroadenomas (20). Those studies, summarized in Table 3, with a follow-up period of 22-73 months, report an increase in tumor size in about 25-50% of the patients However, several aspects of the design of the present study were different from those previous studies. We included all NFMA patients, in whom surgery was not performed for any reason. In contrast to these previous studies, an incidentaloma was the initial finding in only a minority of our patients. Therefore, the characteristics of our study population are different, with a higher prevalence of pituitary insufficiency and visual field defects than those in the previous studies (1,19).

Previous studies also showed that tumor growth does not invariable lead to visual field defects (1,18,20,21). In our series tumor growth (n=14) was accompanied by visual field defects in only 9 patients. Moreover, in only 7 of these patients the pattern was compatible with tumor mass effect. In all patients operated for tumor growth and visual field defects, these defects improved or normalized. These data suggest that in case of the development of visual field defects in the course of NFMA, surgical outcome still is favourable with respect to visual field defects. These results are in accordance with observations in surgical series, which documented improvement of visual field defects in 80% of NFMA patients after transsphenoidal surgery (3,6).

In pituitary microadenomas in general, tumor growth is observed in only a minority of the patients, in contrast to NFMA. Moreover, in microadenomas, the chance of tumor growth seems to be almost outweighed by the change of a decrease in tumor size (1,20). In patients with NFMA the tumor already has demonstrated a propensity for growth. Nonetheless, after a mean follow-up period of 85 months no tumor growth could be detected in this study in 50% of cases. However, at initial presentation, the rate of tumor growth cannot be predicted in individual patients. In our study, no independent predictors for increase or decrease in tumor volume could be found by binary logistic regression.

In patients with NFMA, it is a reasonable approach to repeat MR imaging one year after initial diagnosis, in order to make a first estimation of tumor growth. In our study, in patients with tumor growth, the mean increase in diameter was only 0.6 mm/year, which is below the detection limit of MRI. These data suggest that, for further follow-up, an approach with a repeat MRI every second year is safe and optimal for detection of possible tumor growth.

Diagnostic accuracy might be a limitation of this study, because, in strict sense, pituitary adenoma is a histopathological diagnosis and a number of other sellar lesions may mimic pituitary adenomas, such as germinomas, craniopharyngiomas, meningiomas, sarcoidosis and lymphocytic infiltration (26). However, there are, in addition to the absence of hormone overproduction, arguments that in our series the vast majority of the lesions consist of NFMA. In autopsy series pituitary lesions turn out to be nonfunctioning adenomas in about 50%, the other 50% mainly being hormonal active adenomas (2,27). Moreover, in the vast majority of patients, MRI can with adequate accuracy differentiate between pituitary adenomas and craniopharyngiomas (28,29), and between pituitary adenoma and pituitary hypertrophy (30).

The possibility of pituitary apoplexy must be taken into account in the discussion of surgical versus conservative management of nonfunctioning macroadenomas. Apoplexy is a clinical syndrome resulting from acute haemorrhage or infarction of the pituitary tumor (31). In unselected patients with NFMA, apoplexy is the presenting sign in 15-25% of the patients (13,32). Only a minority of patients presenting with apoplexy were known to harbour a pituitary tumor (33). In contrast, the incidence of apoplexy in patients already known to have a pituitary tumor is estimated to be less than 1%/year (20). In patients with macroadenomas the incidence of apoplexy is probably higher (21). The occurrence of pituitary apoplexy has been described following pituitary function tests (34), coronary artery bypass surgery (33,35), cholecystectomy (36), head trauma (37) and vaginal delivery (38). Moreover, apoplexy has been associated with hypertension (33) and anticoagulant therapy (38). The majority of patients with pituitary apoplexy present with ACTH-deficiency (33), establishing the potential life threatening condition of the clinical syndrome. In the present series 4 patients presented with pituitary apoplexy. In 3 of these cases apoplexy was accompanied by visual field defects, and one patient had multiple pituitary deficiencies. During follow-up both the visual field defects as well as the pituitary deficiencies resolved within three months. Although the optimal treatment for NFMA patients presenting with pituitary apoplexy is still a matter of debate (39-41), surgical intervention is indicated in patients presenting with total or near-total visual loss. After transsphenoidal surgery visual impairment and ocular paresis resolves in the majority of cases (39-41). However, conservative management with careful follow-up, seems appropriate in selected patients without, or with only mild neuro-ophtalmic signs, without adversely affecting patient outcomes (33,39).

In conclusion, our series with non-operated NFMA patients report an increase in tumor size in 50% of all patients during long-term follow-up, accompanied by visual field defects in 50% of these cases. In patients with an increase in tumor size and visual field defects, surgical treatment resolved the visuals field defects. No independent predictors for tumor growth were found by logistic regression. Based on these data, we propose a conservative approach in selected patients with NFMA without visual field defects. In these patients, this is a safe alternative for transsphenoidal surgery, without the risk of irreversibly compromising visual field defects.

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Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma

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CHAPTER 3

SUMMARY

Objective: Transsphenoidal surgery is the treatment of choice for nonfunctioning pituitary macroadenomas (NFMA). In this study we evaluated the long-term effects of a treatment strategy in which postoperative radiotherapy was not routinely applied to patients with NFMA.

Design: Retrospective follow-up study

Patients: We included 109 consecutive patients (age 56 ± 13 years) operated for NFMA between 1992 and 2004.

Results: Radiological imaging revealed a macroadenoma in all patients, with suprasellar extension in 96% and parasellar/infrasellar extension in 36% of cases. Visual field defects were present in 87% of the patients and improved in 84% of these patients after surgery. Only six patients received postoperative radiotherapy. Ten patients died during the follow-up period. Ninety-seven patients could be assessed for tumor regrowth or tumor recurrence after a mean follow-up period of 6.0 ± 3.7 years. In nine patients there was evidence for tumor regrowth, and in one patient tumor recurrence was observed. The mean time to tumor growth/recurrence after initial therapy was 6.9 (range 3-12) years. Follow-up duration was found to be an independent predictor for tumor regrowth.

Conclusion: Transsphenoidal surgery without postoperative radiotherapy is an effective and safe treatment strategy for NFMA, without evidence for tumor regrowth in 90% of all patients, at least for the duration of follow-up presented in this study. Additional studies are required to exclude higher regrowth and recurrence rates during prolongation of the duration of follow up.

INTRODUCTION

Nonfunctioning pituitary macroadenomas (NFMA) are the most prevalent macroadenomas (1;2). The main presenting symptoms of NFMA are visual field defects and hypopituitarism due to mass effects. Transsphenoidal surgery is the treatment of choice because medical treatment in general is not effective in reducing the size of NFMA. However, during long-term follow-up after transsphenoidal surgery, there is tumor growth in 12-46% of the patients (3-6). Therefore, some centers provide postoperative radiotherapy in a selection of the patients to prevent tumor regrowth (6-9). Nonetheless, even after postoperative radiotherapy, tumor regrowth was reported in 2-36% of the radiated patients (4-6;9). In addition, radiotherapy induces a higher incidence of hypopituitarism during long-term follow-up (10-12) and is associated with rare complications such as secondary brain tumors (13). Therefore, a restrictive indication for postoperative radiotherapy seems appropriate.

Prospective trials evaluating the effect of postoperative radiotherapy on regrowth rates of NFMA have not been published. Retrospective studies, involving homogeneous cohorts of transsphenoidal operated NFMA with a long follow-up period, are scarce (3-6;9;14;15). Only two studies have been published in consecutive NFMA patients with a wait and see policy after transsphenoidal surgery. These studies, comprising of 71 and 51 patients respectively, report tumor growth in 21 and 26% during long term follow-up (3;15). However, these reports do not propose a wait-and-see policy for all NFMA patients. The aim of the present study was to evaluate the long-term effects of a wait-and-see policy after transsphenoidal surgery for NFMA on tumor recurrence rates in an unselected, homogeneous, single center cohort of 109 consecutive patients operated for NFMA. Postoperative radiotherapy was applied only in six of the 109 patients.

PATIENTS AND METHODS

Patient selection

Between 1992 and 2004, 109 consecutive patients were treated by transsphenoidal surgery for NFMA (diameter > 1 cm) at the Leiden University Medical Center. All operations were performed by one of two neurosurgeons. For complete assessment of the patients, we reviewed the patient records of all departments involved in the treatment of NFMA. Patients were assessed at presentation prior to surgery, within the first 2 months after surgery, and subsequently every 6 months during prolonged follow-up. Clinical characteristics, visual field defects, pituitary function and MRI images were assessed. Pre-and post-surgical data were available for all 109 patients. In 97 patients at least two postoperative MRI-scans were available, enabling the evaluation of radiological tumor regrowth or recurrence. Ten patients died during the follow-up period, one post-operatively. The duration of follow up in each patient was determined by the interval between the date of transsphenoidal surgery and the date of the last MRI scan. In six patients postoperative radiotherapy was applied. Patients receiving prophylactic radiotherapy were treated with conventional external radiotherapy. All these patients received 46 Gy. Three patients were treated with 220 degree arc therapy and three patients with three-field arrangement, that included left lateral, right lateral and anterior portals.

NFMA was diagnosed if there was neither clinical nor biochemical evidence of hormonal overproduction and histopathological evaluation revealed an adenoma. Histological examination confirmed the diagnosis of pituitary adenoma in all, except five patients, in whom appropriate histological assessment was precluded due to necrosis of the tumor. Adenomas were classified according to immunohistochemistry as either negative or positive for one or more hormone and/or their subunits.

Definitions

Growth hormone (GH) deficiency was defined as an IGF-1 level below the reference range for age and sex (16) and/or an insufficient rise in GH levels (absolute value < 3 μg/L) after stimulation during an insulin tolerance test. Prior studies demonstrated that patients with multiple pituitary hormone deficiencies, including two or more pituitary hormone deficiencies other than GH deficiency, had a likelihood of approximately 95% of harbouring severe GH deficiency (16-18). Based on these data, we classified patients in whom GH-stimulation test data were lacking but who were deficient in 3 other pituitary axes as being GH deficient. When secondary amenorrhoea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient, when gonadotrophin levels were below the normal post-menopausal range (LH < 10 U/l, FSH < 30 U/l). In men, LH/FSH deficiency was defined, as a testosterone level below the reference range (8.0 nmol/L). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as a basal cortisol level at 8.00 A.M. of < 0.12 μmol/l and/or an insufficient increase in cortisol levels (absolute value < 0.55 μmol/ l) after a corticotrophin releasing hormone stimulation test or insulin tolerance test. Hypopituitarism was defined by the presence of one or more pituitary hormone deficiencies. Diabetes insipidus was defined as polyuria not reacting to fluid restriction but reacting to administration of vasopressin.

The pituitary tumors were assessed by MRI scanning. Tumor extension was classified as suprasellar, parasellar/infrasellar, or combined suprasellar and parasellar/infrasellar extension. MRI imaging was performed in all patients within 6 months following transsphenoidal surgery, for the second time one year later, and subsequently with increasing intervals. Patients were classified according to the post-operative MRI as having residual tumor or not having residual tumor. Patients with uncertain MRI diagnosis with respect to tumor residue were classified as having residual tumor (15). Tumor regrowth was defined as an increase in size of residual tumor. Recurrence was defined as appearance of tumor mass in a patient without residual tumor mass on postoperative MRI.

Ophthalmological evaluation included assessment of visual acuity and visual fields, performed by a Humphrey or Goldmann perimeter before and a few weeks after surgery. Patients who had persistent visual field deficits after surgery or noticed visual disturbances any time during prolonged follow up were re-assessed by the ophthalmologist.

Statistical analysis

The unpaired t-test was used for continuous variables. The χ^2 test and the McNemar test were used for categorical data. Binary logistic regression was performed to explore possible determinants of tumor growth. Tumor regrowth-free survival was analyzed with the method of Kaplan and Meier. SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA) was used. A P-value of < 0.05 was considered statistically significant.

Table 1. Patient characteristics before surgery

Number of patients	109
Mean age (years)	56 ± 13
Male	61/109 (56%)
Clinical presentation	
Visual field defects	90/104 (87%)
Headache	41/105 (39%)
Cranial nerve deficit	8/109 (7%)
Apoplexia	8/101 (8%)
Pituitary deficiencies	
GH deficiency	58/75 (77%)
LH/FSH deficiency	77/103 (75%)
ACTH deficiency	53/101 (53%)
TSH deficiency	45/106 (43%)
Panhypopituitarism	32/109 (29%)
Radiology	
Suprasellar extension	105/109 (96%)
Parasellar/infrasellar extension	39/109 (36%)
Immunohistochemistry	
Positive immunostaining	68/104 (65%)
Silent gonadotropinoma	41/104 (39%)
Silent corticotropinoma	11/104 (11%)
Multiple hormones	9/104 (9%)

RESULTS

Preoperative patient characteristics (Table 1)

The most prevalent presenting symptoms were visual field defects (87%) and headache (39%). NFMA presented as apoplexy in 8 cases. Radiological imaging by MRI revealed a macroadenoma in all patients, with suprasellar extension in 96% and parasellar/infrasellar extension in 36% of cases. Hypopituitarism was present in 80% of all patients and panhypopituitarism in 29%.

Surgical treatment

All patients were treated by transsphenoidal surgery. One patient died of subarachnoidal bleeding two days after surgery, resulting in a perioperative mortality rate of 0.9%. Repeat surgery within 6 months after initial treatment was performed in 6% of cases (n=7), for a large residual tumor mass (n=4), persisting liquor leakage (n=2) and profuse bleeding (n=1). Repeat surgery was performed by transcranial approach, except in the two patients with leakage of cerebrospinal fluid.

Transsphenoidal surgery was followed by radiotherapy in six patients. The decision to apply prophylactic radiotherapy was based on the presence of a large residual tumor (n=3) or a residual tumor with strongly positive immunostaining for ACTH (n=3).

Immunohistochemistry could be assessed in 95% of cases and was positive in 65%. Off all cases, 39% harboured a silent gonadotrophic adenoma, 11% a silent corticotrophic adenoma, and 9% was immunoreactive for multiple hormones.

Post-operative MRI revealed residual tumor in 73% of all cases.

Table 2. Effect of transsphenoidal surgery on pituitary function

Deficiency	Pre-operative	Post-operative	p-value
GH deficiency	58/75 (77%)	76/92 (83%)	ns
LH/FSH deficiency	77/103 (75%)	95/106 (90%)	< 0.01
ACTH deficiency	53/101 (53%)	65/108 (60%)	ns
TSH deficiency	45/106 (43%)	61/107 (57%)	< 0.05

Post-operative evaluation: visual field defects and pituitary deficiencies (Table 2)

Visual field deficits improved in 84% of cases after surgery (complete recovery 21%; partial recovery 63%). Visual field defects stabilized in 13% and deteriorated in only three patients after surgery.

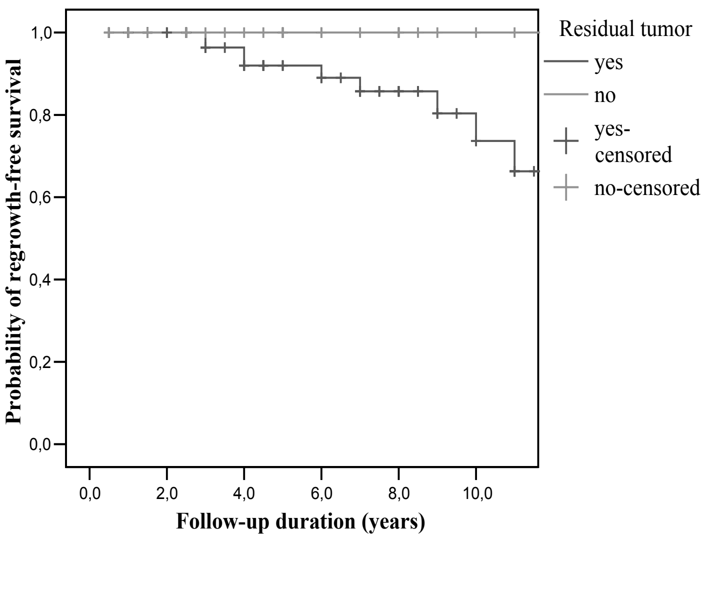
After surgical treatment 90% of the patients were LH/FSH deficient, 83% GH deficient, 60% ACTH deficient and 57% TSH deficient. Hypopituitarism was present in 95% of cases and panhypopituitarism in 44%. When compared with the pre-surgical data, surgery significantly increased LH/FSH ($P<0.01$) and TSH deficiency ($P<0.05$) as well as panhypopituitarism ($P<0.001$). Pre-operative prolactin levels < 2 µg/L (n=19) were not associated with significant higher rates of pre-operative or post-operative pituitary deficiencies. Transient diabetes insipidus occurred in 28% of cases. After surgery there was a significant decrease in prolactin levels in both women and men ($p<0.01$). In women mean prolactin decreased from 29.1 ± 25.3 µg/L to 9.4 ± 9.1 µg/L; in men from 14.1 ± 13.7 µg/L to 4.3 ± 3.3 µg/L.

Long-term post surgical follow-up (Figure 1)

Ninety-seven patients could be assessed for recurrence with a mean follow-up period of 6.0 ± 3.7 years and a median follow-up period of 5.0 years (range 1-14 years). Residual tumor was present in 70 patients. Six of the 97 patients had received postoperative radiotherapy.

Long-term tumor control of NFMA in our series was achieved in the absence of regrowth/recurrence in 90% of all patients. Tumor regrowth was observed in 9 patients, after a mean follow-up of 6.3 years (Range 3-11 years). In one patient, initially classified as 2B macroadenoma, recurrence occurred after 12 year follow-up. In the six patients treated with prophylactic radiotherapy no tumor regrowth was observed. For the total cohort the tumor growth free survival rates, 5 and 10 years after initial surgery, were 94% and 81%. In patients with residual tumor on MRI, regrowth free survival rates 5 and 10 years after initial surgical treatment, were 92% and 74% (Figure 1). In patients without

Figure 1. Kaplan Meier curve for growth-free survival rates in patients with and without residual tumor



residual tumor, recurrence free survival rates 5 and 10 years after initial surgical treatment were 100% and 100%.

Tumor regrowth was associated with an increase in visual field defects in 4 patients. Tumor regrowth and recurrence were treated by radiotherapy (n=9) and by repeat surgery followed by radiotherapy (n=1).

Binary logistic regression analysis was performed to determine possible independent predictors for tumor growth. The following parameters were evaluated: gender, prophylactic radiotherapy, follow-up duration, any positive immunohistochemistry, positive immunohistochemistry for ACTH, parasellar/infrasellar tumor extension and residual tumor on MRI. Follow-up duration was the only independent predictor ($P<0.05$) for tumor growth. Although analysis pointed towards residual tumor as an independent predictor for regrowth, this did not reach statistical significance ($P=0.1$).

Ten patients died during the follow-up period. The main causes of death were malignancy (n=3), cardiovascular disease (n=2) and cerebrovascular disease (n=2). There where no deaths due to cerebral malignancies.

DISCUSSION

This study demonstrates that transsphenoidal surgery without postoperative radiotherapy is an effective and safe treatment strategy for NFMA, at least for the duration of follow up presented in this study. Long-term tumor control of NFMA in our series was achieved in the absence of regrowth/recurrence in 90% of all patients. Even in the case of residual tumor, in 87% no tumor regrowth was observed. These data, observed after six years of follow-up, do not justify prophylactic postoperative radiotherapy. Moreover, even in the case of regrowth during long-term follow-up, radiotherapy is still effective to stabilize or regress tumor growth (5). With this restrictive treatment strategy, the majority of patients will not be exposed to potential long-term sequelae of radiotherapy, whereas in patients with recurrences, the starting point of radiotherapy is delayed for several years.

Six patients received post-surgical radiotherapy, because of large residual tumor (n=3) or residual tumor with strongly positive immunostaining for ACTH (n=3). The reason for radiotherapy in ACTH-positive tumors was mainly historical. Previous studies proposed that there was a higher regrowth rate in ACTH-positive tumors (14;19). However, in a recent study from Bradley *et al,* positive immunostaining for ACTH did not seem to increase recurrence rates (20). In the worst-case scenario, in case the six patients would have developed tumor regrowth without radiotherapy, the rate of patients without tumor regrowth or recurrence in our series would still be 85%. Moreover, even if tumor growth occurred in 15% of all patients, this does not justify prophylactic postoperative radiotherapy.

Table 3. Effect of transsphenoidal surgery in NFMA on pituitary function

	Arafah *et al.* (22)	Comtois *et al.* (3)	Marazuela *et al.* (21)	Greenman *et al*. (23)	Wichers-Rother *et al.* (26)	Nomikos *et al.* (24)	Alameda *et al.* (8)	Present series
Patients (n)	26	126	35	26	109	660	51	109
Clinical symptoms								
Visual field defects (%)	73	78	60	ND	63	31	62	87
Tumor characteristics								
Suprasellar extension (%)	80	94	80	96	ND	ND	82	96
Parasellar/infrasellar extension (%)	ND	33	84	42	ND	ND	48	36
Pituitary: pre-operative function								
GH deficiency (%)	100	ND	88	ND	85	ND	80	77
LH/FSH deficiency (%)	96	75	69	78	61	77	62	75
TSH deficiency (%)	81	18	23	23	31	19	21	43
ACTH deficiency (%)	62	36	29	43	32	35	19	53
Hypopituitarism (%)	ND	73	69	89	ND	85	85	83
Pituitary: postoperative function								
GH deficiency (%)	85	ND	82	ND	78	ND	88	83
LH/FSH deficiency (%)	65	70	48	46	50	65	57	90
TSH deficiency (%)	35	31	20	12	34	16	27	57
ACTH deficiency (%)	38	29	13	50	25	18	19	60
Hypopituitarism (%)	ND	ND	ND	65	ND	72	89	94

ND denotes not documented

Table 4. Effect of transsphenoidal surgery with/without postoperative radiotherapy (RT) on tumor growth in selected NFMA-series

Study	Number of patients	Follow-up (years)	Invasive tumor (%)	RT (%)	Tumor growth (%)		5 yr growth free survival (%)		10 yr growth free survival (%)	
					RT yes	RT no	RT yes	RT no	RT yes	RT no
Bradley *et al.* (28)	73[a]	ND[b]	[c]	0	-	11	-	90	-	ND
Lillehei *et al.* (29)	32[d]	5.5	ND	0	-	6	-	94	-	ND
Turner *et al.* (30)	65[e]	6.3	ND	0	-	32	-	82	-	56
Scheithauer *et al.* (14)	23[f]	4.9	30	48[g]	54[h]		ND		ND	
Bradley *et al.* (20)	28[i]	7.4	32	18	20	35	ND	ND	ND	ND

[a] Only non-irradiated patients included
[b] ND denotes not documented
[c] Only patients without locally invasive tumors included
[d] Only patients included in which gross removal of the tumor was achieved
[e] Same study-cohort as Bradley et al. 1994 (28), however with longer follow-up
[f] All with ACTH positive immunostaining
[g] Radiotherapy was applied when residual tumor was present
[h] No separated data for patients with and patients without radiotherapy available.
Only calculated for patients with follow-up > 3 years, and recurrence defined as persistent tumor or regrowth
[i] All with ACTH positive immunostaining

Perioperative mortality was minimal in our series (0.9%) and comparable with those reported in other studies (3;4;7). Visual field defects improved in more than 80% of the patients, which is comparable with other studies in which improvement of visual field defects have been reported in 75-100% (3;4;14;21). Surgical treatment in our study did not reverse pituitary deficiencies. We summarized previous studies on the effect of transsphenoidal surgery on pituitary function in NFMA in Table 3 because the data of these studies are conflicting. Some studies report, to a variable degree, an improvement in pituitary function (21-25), whereas others could not demonstrate significant improvement in pituitary function (3;9;26) or even reported a decrease in pituitary function (8;27). Therefore, the aim of transsphenoidal surgery should be improvement of visual field defects, rather than improvement of pituitary function.

We found 11 previous studies that evaluated the effects of long-term follow up after transsphenoidal surgery, with and/or without postoperative radiotherapy, on tumor control of NFMA. These studies are all retrospective studies like our study. These studies differed with respect to the selection of patients with NFMA. In 5 studies results of long-term follow-up in selected, non-consecutive groups of patients after surgery for NFMA are presented (Table 4, (14;20;28-30)). In those studies, patients were selected from postoperative patients with NFMA only if they had not received radiotherapy and did not have locally invasive tumors (28;30), only if gross removal of the tumor was achieved (29), or only if immunostaining was positive for ACTH (14;20). During long term follow up without postoperative radiotherapy, tumor growth rates in those studies ranged between 6 and 35% (20;28-30). Postoperative radiotherapy for NFMA with positive immunostaining for ACTH resulted in a regrowth rates of 20% *versus* 35% without radiotherapy (20).

In Table 5, we have summarized other seven studies (including our study), which evaluated the effects of long-term follow-up in unselected, consecutive patients after surgery for NFMA (3-6;9;15;29).In some of these studies (5;9) postoperative radiotherapy was applied in a small number of patients. The main problem in the interpretation of the therapeutic value of postoperative radiotherapy is that the indications for postoperative radiotherapy were not clearly defined in some of the studies (6;9). The study of Park *et al.* provided postoperative radiotherapy, when tumor removal was incomplete (5). Regrowth rates in patients without postoperative radiotherapy ranged between 11 and 46%, whereas regrowth rates after postoperative radiotherapy ranged between 2-36% during long term follow up. There is a suggestion of a benefit of postoperative radiotherapy on long term tumor recurrence in some (5;6) but not in all studies (4). Therefore, the true benefit of postoperative radiotherapy is not straightforward in individual patient care. Finally, from Tables 4 and 5 it becomes evident that the average duration of follow-up in all series is limited to only 4.3-7.4 years after surgery. Prolongation of the follow-up duration may result in a higher rate of recurrence or regrowth than appreciated by the currently available data.

Table 5. Effect of transsphenoidal surgery with/without postoperative radiotherapy (RT) on tumor growth in unselected NFMA series

Study	Number of patients	Follow-up (years)	Invasive tumor (%)	RT (%)	Tumor growth (%)		5 yr growth free survival (%)		10 yr growth free survival (%)	
					RT yes	RT no	RT yes	RT no	RT yes	RT no
Ebersold *et al.* (4)	100	6.1	ND	58	18	12	ND	ND	ND	ND
Comtois *et al.* (3)	71	6.4	33	0	-	21	-	ND	-	ND
Woollons *et al.*(6)	72[a]	5.3	38	69[b]	26	46	72	34	ND	ND
Soto-Ares *et al.*(15)	51	5.6	59	0	-	26[c]	-	74[d]	-	ND
Greenman *et al.*(9)	122	4.3	64	12[e]	36	43	48		ND	
Park *et al.* (5)	176	4.3	27	25[f]	2	20	98	85	98	50
Present series	109	6.0	36	6	0	11	100	94	100	79

[a] Four patients were operated by transcranial approach
[b] Reasons for radiotherapy unclear
[c] 26% for the total cohort, 38.2% in patients with post-operative tumor residue, 0% in patients without post-operative tumor residue
[d] 74% for the total cohort, 60.9% in patients with post-operative residual tumour
[e] Reasons for prophylactic RT where mainly historical
[f] Radiotherapy was added when tumor removal was incomplete.

The possible benefit of postoperative radiotherapy, *i.e.* a decrease in long-term regrowth rate of NFMA, has to be balanced against potential side effects of radiotherapy. The contribution of postoperative radiotherapy to the development of pituitary deficiencies is independent of tumor regrowth (10-12). Increased mortality is reported in patients with hypopituitarism, compared with age-matched controls (31-34). In addition to very rare complications such as optic nerve atrophy and visual deterioration (12;35;36), there is about 2.5% cumulative risk of second brain tumors 20 year after radiotherapy (13;37). Finally, there are indications that radiotherapy for pituitary adenomas may adversely affect quality of life (38). Nonetheless, postoperative radiotherapy might be considered in selected patients with incomplete tumor removal, large residual tumor and panhypopituitarism.

Tumor regrowth occurred in nine patients, and tumor recurrence in only one patient. In only four of these patients, increase in tumor volume was accompanied by visual field defects. This indicates, that in a ‘wait-and-see-policy’, MRI-scanning is the principal method for detection of tumor regrowth/recurrence because ophthalmologic assessment can still be normal at the time tumor growth can already be detected by MRI.

In conclusion, transsphenoidal surgery for NFMA is a safe and effective procedure, without evidence for tumor growth in 90% of all patients after six years follow-up. Based on the data presented in this study, we advocate a postsurgical wait-and-see procedure, which will prevent unnecessary exposure to potential sequelae of radiotherapy in the majority of patients. Additional studies are required to assess tumor control during prolongation of the duration of follow-up.

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Progressive improvement of impaired visual acuity during the first year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma

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CHAPTER 4

SUMMARY

Objective. Improvement of visual field defects continues even yr after the initial surgical treatment. Because this process of continuing improvement has not been documented for visual acuity, we audited our data to explore the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

Design. Retrospective follow-up study

Patients. Forty-four patients (mean age 56 ± 14 yr), treated by transsphenoidal surgery for nonfunctioning pituitary macroadenoma, were included in this analysis.

Results. Visual acuity improved significantly within three months after transsphenoidal surgery. The mean visual acuity increased from 0.65 ± 0.37 to 0.76 ± 0.36 ($p<0.01$) (right eye), and from 0.60 ± 0.32 to 0.82 ± 0.30 ($p<0.01$) (left eye). Visual acuity was improved one year after transsphenoidal surgery compared to the three months postoperative values. The mean visual acuity increased from 0.76 ± 0.36 to 0.82 ± 0.34 ($p<0.05$) (right eye), and from 0.82 ± 0.30 to 0.89 ± 0.27 ($p<0.05$) (left eye).

Conclusion. Visual acuity improves progressively after surgical treatment for nonfunctioning pituitary macroadenomas, at least within the first year after transsphenoidal surgery.

INTRODUCTION

Nonfunctioning pituitary macro-adenomas (NFMA) are the most prevalent macro-adenomas (1;2). Patients with NFMA mainly present with decreased visual acuity, visual field defects and hypopituitarism, caused by mass effects of the tumor (3-5). Transsphenoidal surgery is the treatment of choice, resulting in improvement of visual field defects in 75-100% of all patients (3-5). Accordingly, visual acuity improves in the majority of patients (6-10), although visual field defects and visual acuity may worsen in a limited number of patients after surgery (6;7;9;10).

The process of visual field recovery starts directly after surgery and can already be documented on the second postoperative day (11). This process of recovery is probably due to restoration of the velocity of conduction. However, improvement of visual field defects continues even yr after the initial surgical treatment (12;13). Although a reduced visual acuity is correlated with the extent of visual field defects (13;14), postoperative changes in visual acuity do not parallel changes in visual fields in every case (6).

To our knowledge, the process of gradual visual improvement has only been observed for visual field defects, but not for visual acuity (12). This is, however, clinically relevant since improvement of minor visual field defects can occur unnoticed, whereas improvement in visual acuity is almost invariably noticed, and can potentially overcome thresholds to previous impairments in daily life. We therefore audited our data to explore the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

PATIENTS AND METHODS

Patient selection

Forty-four patients, mean age 56 ± 14 yr, were included in this retrospective analysis. In order to obtain a homogenous cohort for assessment, the inclusion criteria were the following:

1. Transsphenoidal surgery for nonfunctioning pituitary macroadenoma (diameter > 1 cm) for compression of the optic chiasm
2. Assessment of visual acuity at least once before surgery and at least twice in the first year after surgery
3. The availability of two postsurgical MR scans within a time frame of maximal three months of the ophtalmological assessments

To overcome the potential effect of postoperative tumor-regrowth on visual outcome, patients were excluded from analysis if the one-year post-operative scans revealed growth of residual tumor.

For complete assessment, we reviewed the patient records of all departments involved in the treatment of NFMA (Endocrinology, Neurosurgery, Ophthalmology). Endocrine (pituitary function) and ophthalmologic data (visual acuity and visual fields) were assessed before surgery, 3, and 12 months after surgery. An MRI was performed before surgery, 3-6 months, and 12-15 months after surgery. Transsphenoidal surgery was performed by one of two neurosurgeons.

Corrected visual acuity was determined by the Snellen chart (15;16) and was scored for both eyes. Visual fields were assessed by Humphrey perimetry in all patients. Goldman perimetry was used as an additional tool to assess peripheral visual field defects.

Definitions

The diagnosis of nonfunctioning pituitary macroadenoma was based on two criteria: 1) the presence of a pituitary macroadenoma (>1cm) on MRI, 2) the absence of overproduction of any of the pituitary hormones. In all cases the diagnosis was histological confirmed. Tumor extension was classified as suprasellar, parasellar/infrasellar or combined suprasellar and parasellar/infrasellar extension.

In all patients, visual acuity was scored on a scale between 0 and 1.25. Visual field defects were scored semi-quantitative and classified as mild, moderate or severe. Visual field defects were classified as mild, if there were peripheral defects in only one quadrant. Defects were classified as moderate if the upper quadrants were affected, whereas in combined upper and lower quadrant field defects these were classified as severe.

Growth hormone (GH) deficiency was defined as an insufficient rise in GH levels (absolute value < 3 µg/L) after stimulation during an insulin tolerance test (ITT). When secondary amenorrhoea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient when gonadotropin levels were below the normal post-menopausal range (LH < 10 U/l, FSH < 30 U/l). In men, LH/FSH deficiency was defined as a testosterone level below the reference range (8.0 nmol/L). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as a basal cortisol level at 8.00 A.M. of < 0.12 µmol/l and/or an insufficient increase in cortisol levels (absolute value < 0.55 µmol/ l) after an ITT.

Statistical analysis:

The paired t-test was used for paired samples. SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA) was used. A P-value of < 0.05 was considered statistically significant.

RESULTS

Preoperative patient characteristics (Table 1)

Forty-four patients, 52% male, were included in this study. Radiological imaging by MRI revealed a macro-adenoma in all patients with suprasellar extension in 100% and parasellar/infrasellar extension in 41% of cases. Hypopituitarism was present in 80% of all patients and panhypopituitarism in 25%.

Preoperative assessment of visual function (Table 1)

Visual fields were normal in 9% (5/44) off all patients. Transsphenoidal surgery in these patients was performed for apoplexia (n=1) and because compression of the optic chiasm was evident on the MR scan (n=4). Of all patients with visual field defects 59% were classified as severe, 17% as moderate, and 12% as mild. Mean visual acuity was 0.65 ± 0.37 for the right eye, 0.60 ± 0.32 for the left eye.

Visual acuity was assessed twice before surgery in 34 patients (77% of total). The median time between the first and the second pre-surgical assessment was 4 weeks (range 1-45). No significant decrease in visual acuity was observed within this time period. The mean visual acuity for the two pre-surgical assessments was: 0.65 ± 0.37 vs 0.66 ± 0.38 (right eye), and 0.60 ± 0.32 vs 0.62 ± 0.33 (left eye). Moreover, no decrease in visual acuity was observed in patients (n=13) with a time interval of > 8 weeks between the first and the second pre-surgical assessment.

Table 1. Patient characteristics before transsphenoidal surgery

Male/female	23/21
Age (yr ± SD)	56 ± 14
Visual acuity	
Oculus dexter (mean ± SD)	0.67 ± 0.37
Oculus sinister (mean ± SD)	0.61 ± 0.33
Visual field defects	
Severe	59%
Moderate	17%
Mild	12%
None	12%
Pituitary function	
GH deficiency	77%
LH/FSH deficiency	71%
ACTH deficiency	45%
TSH deficiency	38%
Panhypopituitarism	25%
MRI characteristics	
Suprasellar extension	100%
Infrasellar/parasellar extension	41%

Surgical treatment

All patients were treated by transsphenoidal surgery. Repeat surgery within 6 months after initial treatment was performed twice (large residual tumor mass (n=1) and persisting liquor leakage (n=1)). Repeat surgery was performed by transcranial approach.

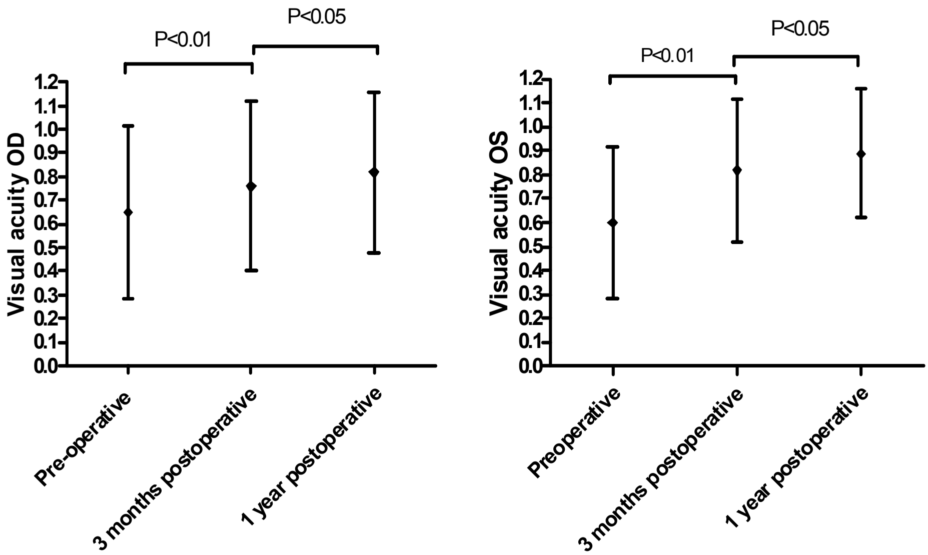
Transsphenoidal surgery was followed by radiotherapy in 10 patients in order to prevent recurrence. Patients received 40 Gy (n=5) or 46 Gy (n=5).

Three months postoperative assessment of visual function

After transsphenoidal operation in patients with preoperative visual field defects improvement was observed in 60% and normalisation of the visual fields in 32%. In 1 patient there was a slight increase in visual field defects.

Visual acuity improved significantly three months after transsphenoidal surgery (Figure 1). The mean visual acuity increased from 0.65 ± 0.37 to 0.76 ± 0.36 ($p<0.01$) (right eye), and from 0.60 ± 0.32 to 0.82 ± 0.30 ($p<0.01$) (left eye).

Figure 1. The pattern of improvement of visual acuity after transsphenoidal surgery for nonfunctioning pituitary macroadenomas (n=44)



One-year postoperative assessment of visual function

One year after initial surgical therapy visual field defects showed continuous improvement in 35% patients, compared with early postoperative results. In 80% of these patients, this improvement was accompanied by continuous improvement of visual acuity.

In 55% of all patients (n=24), visual acuity shows continuing improvement until one year after surgery. In 8 of them, this improvement was not accompanied by further improvement of visual field defects. Visual acuity was improved one year after transsphenoidal surgery compared with the three months postoperative values (Figure 1). The mean visual acuity increased from 0.76 ± 0.36 to 0.82 ± 0.34 ($p<0.05$) (right eye), and from 0.82 ± 0.30 to 0.89 ± 0.27 ($p<0.05$) (left eye).

DISCUSSION

The main aims of surgery in nonfunctioning pituitary macroadenomas are restoration of visual acuity and visual field defects by decompression of the optic chiasm. Nonetheless, our data indicate that there is no necessity for immediate decompression since postponement of surgery for several weeks did not result in deterioration of visual acuity. Moreover, in this series of 44 patients, we demonstrated a continuing improvement of visual acuity until one year after transsphenoidal surgery.

There is a significant correlation between the severity of visual loss prior to surgery and persisting visual field defects (9;13;14). In our patients in whom visual acuity was assessed twice before surgery, no decrease of visual acuity was observed with a median time interval between two measurements of 4 weeks. This indicates that postponing surgery for one month does not negatively influence visual outcome, which is in line with the slow growth pattern of nonfunctioning adenomas (4). Nonetheless, the delay of surgery should not unnecessarily be prolonged because a significant, inverse, correlation between visual outcome and the prolonged duration of symptoms has been reported (9).

The initial event in the pathogenesis of decreased visual function in pituitary macroadenomas is compression of the optic chiasm. Nerve compression leads to decreased conduction and demyelination. In an experimental setting, the process of demyelination after nerve compression has been observed even after two days (17;18). In case of continuous nerve compression remyelination can be observed after several weeks, although remyelinated fibres do not seem to reach normal thickness and organisation structure, and complete demyelinated fibres co-exist (17;18). Re-myelinated fibers restore conduction, at least partially, even if the causative nerve lesion is still existing (19;20). The improvement of visual dysfunction after surgical treatment is supposed to consist of two, or probably even three, phases (12). There is an early phase, comprising the first hours and days after surgery. In this early fast phase, the improvement is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual recovery has been demonstrated in the first days after surgical treatment (11;12). The second phase, i.e. delayed recovery, is pathophysiologically caused by restoration of axonal transport and remyelination and based on remyelination of the optic nerve vessels. This phase of delayed recovery may last for several yr (12;13). A precise boundary between the end of the fast phase of recovery and the start of the delayed recovery seems to be artificial, because these two phases reflect different pathophysiological mechanisms, which may co-exist for a certain time-period. The contribution of the first phase of recovery might be larger, given the fact that more than 50% of eventual recovery takes place within the first three months after surgery (13).

It is already known that visual acuity improves in the first months after surgical treatment (6-10) and that the improvement of visual field defects is a continuing process for at least one year (12;13). Kerrison *et al.* (12) showed progressive improvement of visual fields even more than two yr after surgical decompression of the optic chiasm. However, they did not demonstrate this same pattern of recovery for visual acuity. This might be due to the relative small number of patients during prolonged follow-up. In the present study we demonstrate that also improvement of visual acuity continued one year after surgical treatment.

The clinical consequences of the delayed phase of recovery for both visual field defects and visual acuity are obvious. Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmologic assessment within several weeks after surgery, as well as subsequent assessments after one and two years, in order to estimate the final effect of surgery on visual function. Moreover, patients should be told that visual function can continue to improve at least until one year after surgery. The relevance of these findings is obvious and is of importance to all patients, given the impact of a decreased visual acuity as an independent predictor for a decreased quality of life (21;22). Moreover, these data are essential in order to evaluate potential effects of recurrent pituitary adenomas on visual function.

Ten patients in our series received postoperative radiotherapy. However, it is unlikely that this treatment affected the results of our study. In a series reported by Gnanalingham *et al.* (13), in which 34% of all patients received postoperative radiotherapy, persistent improvement of visual field defects was documented even yr after surgical therapy. In another series of 21 patients, 2 yr after pituitary irradiation, there were no cases of radiation-induced visual field or visual acuity deterioration (23).

In conclusion, this study demonstrates that the improvement of visual acuity after transsphenoidal treatment for nonfunctioning pituitary macroadenomas consists of both an early and a delayed phase of recovery. After initial post-surgical recovery, a progressive delayed improvement of visual acuity at least until one year after transsphenoidal surgery is likely to occur.

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The relative risk for mortality in patients treated for Cushing's disease is increased compared with patients treated for nonfunctioning pituitary macroadenoma

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CHAPTER 5

SUMMARY

Objective. Several studies have reported increased mortality in patients with pituitary tumors after surgical treatment. However, it is presently unknown to what extent this excess mortality is caused by pituitary tumors and their treatment in general, and to what extent by previous exposure to hormonal overproduction. The aim of the present study was to compare relative mortality risks between patients previously treated for Cushing's syndrome and for nonfunctioning pituitary macroadenomas.

Patients and Methods. We included 248 consecutive patients with pituitary adenomas treated by transsphenoidal surgery in our hospital for nonfunctioning pituitary macroadenomas (NFMA) (n=174) and ACTH producing adenomas (n=74). The standardized mortality ratio (SMR) was calculated for the whole cohort, as well as for the two diseases separately. Cox regression analysis was used to estimate the relative risk for mortality of patients with Cushing's disease compared with NFMA patients.

Results. The mean duration of follow up after surgery was 10.1 ± 7.2 years for the whole cohort. Patients with Cushing's disease (39.1 ± 16.1 yr) were significantly younger at time of operation than patients with NFMA (55.3 ± 13.4 yr).The SMR for the whole cohort was 1.41 (95% CI 1.05-1.86). The SMR in NFMA patients was 1.24 (95% CI 0.85-1.74) versus 2.39 (95% CI 1.22-3.9) in patients with Cushing's disease. In patients with Cushing's disease, compared with NFMA, the relative age-adjusted mortality risk was significantly increased: 2.35 (95% CI 1.13-4.09, P=0.008).

Conclusion. The relative risk for mortality in patients previously treated for Cushing's disease was increased, compared with NFMA. This implies that previous, transient overexposure to cortisol is associated with increased mortality.

INTRODUCTION

Pituitary adenomas are benign neoplasms associated with considerable morbidity due to mass effects, hormonal overproduction and pituitary insufficiency. In nonfunctioning pituitary macroadenomas (NFMA) morbidity is caused by mass effects of the tumor leading to visual field defects, decreased visual acuity and pituitary insufficiency in the majority of patients (1). In functioning pituitary adenomas morbidity is caused by hormonal overproduction, in addition to tumor mass effects in cases of macroadenomas. In Cushing's disease, cortisol excess causes central obesity, insulin resistance, hypertension, hyperlipidemia and osteoporosis (2;3). Moreover, cortisol overproduction is associated with increased cardiovascular risk, continuing even after remission of the disease (4;5).

In addition to increased morbidity, a number of studies have reported increased mortality in patients with pituitary tumors (6-10) and associated conditions such as hypopituitarism (11-13). In the majority of these studies the general population was used as a control group to assess mortality risk in patients with pituitary adenomas. However, this approach is not able to make a distinction between the effects of hormone overproduction per se versus the general aspects of the pituitary tumor and their treatment, on mortality. Therefore, we performed a single center study to assess mortality ratios during long term follow up after transsphenoidal surgery in patients with nonfunctioning pituitary macroadenomas and Cushing's disease. To answer the question to which extent previous exposure to hormonal overproduction *per se* is associated with increased mortality, we compared mortality in patients operated for Cushing's disease to mortality in patients operated for NFMA.

PATIENTS AND METHODS

Patients

All 248 consecutive patients treated at the Leiden University Medical Center (LUMC) between 1977 and 2005 by primary transsphenoidal surgery for NFMA (n=174) and Cushing's disease (n=83) were eligible for inclusion in the study. The majority of these patients were described in previous studies (1;14). For mortality analysis, information on emigration, death or survival was available for all patients. Nine of the patients with Cushing's disease were excluded from the analysis, because the initial treatment, prior to transsphenoidal surgery, consisted of unilateral adrenalectomy followed by pituitary irradiation. Therefore, we included 74 patients with Cushing's disease in the analysis.

Clinical, endocrinological, visual and radiological preoperative assessment was available for all patients. Clinical, endocrinological and visual characteristics were assessed within the first 2 months after surgery, and, subsequently, every 6-12 months during prolonged follow-up.

Diagnostic criteria and criteria for cure/recurrence

NFMA was diagnosed, if there was a pituitary macroadenoma without clinical or biochemical evidence of hormonal overproduction. The diagnosis of Cushing's disease was made on clinical grounds together with biochemical confirmation, based on the following tests: increased 24 h urinary excretion of free cortisol (24 h UFC, criterion > 220 nmol/24 h), failure of serum cortisol to suppress following low-dose dexamethason (1 mg), suppression of serum cortisol during a 7h intravenous dexamethason suppression test (15), and an normal or exaggerated response of serum ACTH and cortisol to intravenous CRH stimulation (16). In patients with Cushing's disease, in whom a pituitary adenoma was not visualized by MRI, selective inferior petrosal sinus sampling was performed. A central to peripheral ACTH gradient of > 2 (basal) or 3.5 (after CRH) was considered confirmative for an ACTH-producing adenoma.

Tumor recurrence in patients with NFMA was defined as an increase in tumor volume on sequential radiological imaging. Biochemical cure in Cushing's disease was defined as a normal suppression of serum cortisol levels to 1 mg oral dexamethason (cortisol < 100 nmol/L the following morning) and normal 24 urine free cortisol excretion in 2 consecutive samples. Persistent Cushing's disease was defined as a failure to fulfil biochemical criteria for remission 3-6 months after the first operation (14). Relapse of Cushing's disease was defined as recurrence of hypercortisolism, using the abovementioned criteria for Cushing's disease.

Assays

Until 1986 cortisol was measured by in house RIA with an interassay coefficient of variation of 10%. Between 1986 and 1994 a fluorescence energy-transfer immunoassay Syva Advance (Syva Company, Palo Alto, CA) was used, with an interassay variation coefficient of 3.6 to 6.1%. From 1994 cortisol was measured by fluorescence polarisation assay on a TDx (Abbott, Abbott Park, Ill). The interassay variation coefficient is 5-6% above 0.5 µmol/l and amounts to 12% below 0.20 µmol/l.

Hormonal evaluation and treatment

Growth hormone (GH) deficiency was defined by an IGF-1 level below the reference range for age and sex (17), and/or an insufficient rise in GH levels (absolute value < 3 µg/L) after stimulation during an insulin tolerance test (ITT). ACTH deficiency was defined by a basal cortisol level at 8.00 A.M. of < 0.12 µmol/l and/or an insufficient increase in cortisol levels (absolute value < 0.55 µmol/ l) after an insulin tolerance test (ITT: nadir glucose < 2.2 nmol/L). When secondary amenorrhoea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient, when gonadotrophin levels were below the normal post-menopausal range (LH < 10 U/l, FSH < 30 U/l). In men, LH/FSH deficiency was defined by a testosterone level below the reference range (8.0 nmol/L). TSH deficiency was defined as a total or free T4 level below the reference range. In case of ACTH deficiency patients were treated with hydrocortisone (standard treatment regimen: 20mg daily) and TSH deficiency was treated with levothyroxine. In case of LH/FSH deficiency men were substituted with testosterone and women < 50 years with estrogen replacement. From 1994 onwards, patients with documented GH-deficiency were treated with rhGH.

Tumor size classification and radiological follow-up

Radiological imaging was performed by CT (until 1985) and subsequently by MRI. Tumor size was classified according to Hardy (18). For the present study, the classification was simplified to microadenoma (Hardy I ^{0}), noninvasive macroadenoma (Hardy II $^{0, A, B, C}$) and invasive macroadenomas (with suprasellar or parasellar invasive growth; i.e. Hardy II ^{D,E}, Hardy III $^{0-E}$ and Hardy IV^{0-E}). In patients with NFMA imaging was performed within one year after the initial surgical treatment and subsequently MRI scanning was performed every second year. In patients with Cushing's disease repeat radiological imaging was performed in case of persistent or recurrent disease, or, according to the judgement of the treating physician.

Treatment (Table 1)

All 248 patients were operated by transsphenoidal approach. Postoperative, conventional radiotherapy was applied in 50 cases in order to prevent recurrence in NFMA, or to treat persistent active Cushing's disease. Recurrent disease in NFMA was treated by radiotherapy, by repeat surgery, or both. Persistent or recurrent disease in Cushing's disease was treated by bilateral adrenalectomy, radiotherapy, repeat surgery or a combination of these treatment modalities.

Statistics and mortality analysis

We used two different methods to assess mortality in patients with pituitary adenomas. First, we calculated the SMR for the whole cohort, as well as for the two different pituitary diseases included in the study, i.e. NFMA and Cushing's disease. Normal mortality rates for the Dutch population were obtained from the Dutch Central Bureau of Statistics (The Netherlands) using mortality rates per sex, age groups of 5 yr, and calendar periods of 5 yr (1975, 1980, 1985, 1990, 1995 and 2000). Expected mortality rates were determined based on the person-years follow-up for each sex and age group and each calendar period and compared with the observed mortality rate. Second, we used cox-regression analysis to assess the effect of different pituitary adenomas on mortality. The model ad-

Table 1. Treatment characteristics

NFMA (n=174)	
Transsphenoidal surgery	174
Repeat surgery for recurrence	9 (in 5 cases combined with radiotherapy)
Postoperative radiotherapy	63
Prophylactic	42
For recurrence	19
Cushing's disease (n=74)	
Transsphenodal surgery	74
Bilateral adrenalectomy	6
Repeat surgery	10
For persistent disease	4
For recurrence	6
Radiotherapy	14
Prophylactic	1
For persistent disease	7
For recurrent disease	6

justed for sex and age at the time of operation. We did not correct for tumor volume and hypopituitarism, because, although these factors might be associated with mortality, they are closely associated with the underlying diagnosis. Data are expressed as mean ± SD, unless otherwise mentioned. The chi-squared test was used for categorical data.

RESULTS

Patients and treatment (Table 2)

We included 248 consecutive patients in this study, who were transsphenoidally operated for NFMA (n=174) and Cushing's disease (n=74). The mean duration of follow-up for the total cohort was 10.1 ± 7.2 years, comprising a total of 2497 person-years. The mean age at time of operation was significant younger in patients with Cushing's disease (39.1 ± 16.1 yr), compared with patients with NFMA (55.3 ± 13.4 yr, P<0.001). Female gender was more prevalent in Cushing's disease (77%) than in NFMA (44%, P<0.001). All NFMA patients had a macroadenoma, because clinically nonfunctioning microadenomas are in general not operated. Patients with Cushing's disease had a high prevalence of micro-adenomas (85%). Preoperative pituitary insufficiency was significantly more prevalent in NFMA patients (85%), compared with patients with Cushing's disease (5%) (P<0.001).

Treatment and treatment outcome (Table 1)

Long-term tumor control, i.e. the absence of radiological evidence of tumor recurrence, was achieved in 84% of all NFMA patients. Tumor recurrence in NFMA was treated by radiotherapy (n=14), surgery (n=4) or combined surgery and radiotherapy (n=5). In 3

Table 2: Patient characteristics

	Nonfunctioning macroadenoma	Cushing's disease
Number of patients	174	74
Age at operation (yr)	55.3 ± 13.4	39.1 ± 16.1
M/F	98/76	18/56
Mean follow-up (yr)	9.1 ± 6.6	12.8 ± 7.3
Radiological characteristics		
Microadenoma		85%
Non-invasive macroadenoma	70%	11%
Invasive macroadenoma	30%	4%
Pituitary function		
Preoperative pituitary insufficiency	85%	5%
Postoperative pituitary insufficiency	91%	23%
Pituitary insufficiency longest follow-up	95%	44%

other patients a wait and see approach was undertaken after recurrence of the adenoma, because of high age and serious comorbidity.

Eighty % of the patients operated for Cushing's disease achieved initial remission. Eight patients relapsed after initial remission. Persistent disease (n=15) or recurrent (n=8) disease was treated by repeat surgery (n=4), radiotherapy (n=8), or a combination of these treatment modalities with or without adrenalectomy (n=9). In 2 patients a wait-and-see approach was undertaken, because of high age (n=1) and because the patient refused additional treatment (n=1). These two patients were alive at the time of the final evaluation. Long-term remission of Cushing's disease was achieved in 93% of all patients.

Mortality

During a mean follow-up period of 10 years, 47 patients with a mean age 71.1 ± 12.0 years died (NFMA n=35, Cushing's disease n=12). The all cause mortality was 20% in NFMA patients and 16% in Cushing's disease. However, the mean age at death was younger in patients with Cushing's disease (62.4 ± 11.5 yr) compared with patients with NFMA (74.1 ± 10.7 yr, $p<0.05$). Causes of death were cardiovascular disease in 23.4%, cerebrovascular disease in 12.8%, malignancy in 19.1% and infectious diseases in 17% of all patients. The cause specific mortality for NFMA and Cushing's disease is provided in Table 3. One patient with Cushing's disease died because of persistent severe Cushing's disease, despite multimodality treatment.

Standardized mortality ratios (Table 3)

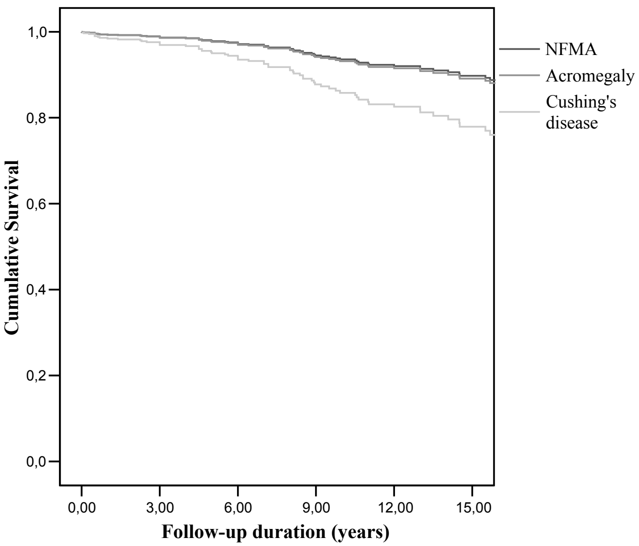
A total of 2497 person-years was available for comparison with normative data of the Dutch population. The SMR for the whole cohort, derived from the observed: expected ratio (47:33.2), was 1.41 (95% CI 1.05-1.86).

The SMR in NFMA patients was 1.24 (95% CI 0.85-1.74), whereas in patients with Cushing's disease the SMR was 2.39 (95% CI 1.22-3.9).

Table 3. Standardized mortality ratios and causes of mortality after transsphenoidal surgery for pituitary adenomas

	Total cohort (n=248)	Nonfunctioning macroadenoma (n=174)	Cushing's disease (n=74)
Number of deaths	47	35	12
Age of dying (yr)	70.5 ± 10.7	74.1 ± 10.7	62.4 ± 11.5
SMR	1.41 95% CI 1.05-1.86	1.24 95% CI 0.85-1.74	2.39 95% CI 1.22-3.9
Causes of death			
Cardiovascular	11	7	4
Malignancies	9	8	1
Infectious	8	7	1
Cerebrovascular	6	5	1
Persistent disease despite multimodality treatment	1		1
Unknown	5	3	2
Other	7	5	2

Figure 1 Mortality in patients treated for nonfunctioning macroadenoma, acromegaly and Cushing's disease (cox-model, corrected for age and gender)



Mortality in Cushing's disease compared with nonfunctioning adenomas (Figure 1)

We performed cox-regression analysis to assess the effect of two different diseases, NFMA and Cushing's disease, on mortality. In the regression analysis we adjusted for age at initial operation, and sex, because age and sex distribution were significantly different between the two study groups. We used the NFMA patients as reference group, and estimated the relative mortality risk of patients with Cushing's disease.

In patients with Cushing's disease, compared with NFMA, the relative mortality risk was significantly increased: 2.35 (95% CI 1.13-4.09, P=0.008). By regression analysis, in a model adjusted for age and gender, radiotherapy and hypopituitarism were not associated with increased mortality risk. The relative mortality risk of patients with Cushing's disease in whom the disease persisted after initial surgical treatment was increased (RR 6.21, 95% CI 1.46-26.4) compared with patients who were cured by initial surgery.

DISCUSSION

In the present single center study we assessed mortality rates during long-term follow up of patients with NFMA and Cushing's disease after treatment by transsphenoidal surgery. The mortality of these patients was increased by 41%, compared with the expected rate of the general population, despite adequate treatment. The relative risk for mortality in Cushing's disease was increased, compared with that in NFMA. Moreover, the mortality risk was increased in patients with persistent Cushing's disease after operation compared with cured patients. This implies that transient overexposure to cortisol is associated with increased mortality, and that mortality risk seems to be correlated with the duration of overexposure to cortisol.

Mortality in pituitary adenomas is associated with general aspects of pituitary tumors and their treatment, but also with disease specific morbidity. We compared patients with Cushing's disease to patients treated for NFMA in order to assess the possible role of hormonal excess in increased mortality, because patients treated for NFMA lack cortisol excess specific for Cushing's disease. The patients presented in this single-center study are comparable in several aspects. First, the time of inclusion was comparable between NFMA and Cushing's disease. Second, all patients underwent transsphenoidal surgery as primary treatment. Third, patients were operated by the same team of neurosurgeons. This is important because treatment outcomes after transsphenoidal surgery have shown to be different among different centers and are dependent on the experience of the surgeon (19). Fourth, all patients underwent the same follow-up and treatment regimen, especially with respect to hormonal substitution. Despite these similarities, patients treated for NFMA still differ from Cushing's disease for relevant factors, in addition to the lack of overproduction to cortisol: size of the adenomas, pituitary insufficiency, age and sexratio. In patients with NFMA, by definition, macroadenomas are more prevalent than in patients with Cushing's disease. Therefore, in most patients the mass effects of the adenomas are greater in NFMA patients, resulting in higher rates of pituitary insufficiency in NFMA than in Cushing's disease. However, this would adversely affect prognosis in NFMA rather than that in Cushing's disease. Therefore, even if adenoma size and pituitary insufficiency would have affected mortality in NFMA patients, this would have decreased, rather than increased, the difference between both patient groups. Finally, Cushing's disease is associated with a much younger age of the patients compared with NFMA and a higher preponderance of female patients. These discrepancies are inherent to the clinical phenotypes of both pituitary diseases. We addressed the confounding affects of differences in age and sex ratios between both patient groups on mortality risk by comparing the mortality rates of both groups separately to the mortality rates per sex and age groups of 5 yr of the Dutch population. By this way, we could compare the mortality risk between NFMA and Cushing's disease despite differences in age and sex ratio.

Contributors to the increased mortality risk in pituitary tumors in general are, factors related to treatment and to hypopituitarism. Transsphenoidal surgery is associated with a peri-operative mortality of only ~ 0.9% (19;20). The peroperative mortality in our study was 0.8% (n=2). Results of the effects of radiotherapy on long-term mortality are conflicting (7;12;21;22). In our study, the application of radiotherapy was not associated with excess mortality. However, this issue requires further investigation, because the comparison between irradiated and non-irradiated patients is not straightforward. Potential bias is introduced because the indication for radiotherapy has changed over time, and a longer period after radiotherapy is required before remission established. Hypopituitarism, present in the majority of patients treated for pituitary macroadenomas, is associated with increased mortality (11;12). Although the exact mechanisms by which hypopituitarism might cause an increase in mortality is unclear, it is suggested that hypopituitarism is associated with premature vascular disease (13;23-25). Several authors point towards the role of untreated GH-deficiency in this respect (13;26).

In our study we found an 1.2 fold increased mortality in NFMA patients compared with the general population, although this difference was not significant. However, mortality was 1.7 fold increased in a larger series with more than 500 NFMA patients (12). In that study, a substantial part of the patients was operated by transcranial approach, which might, at least in part, account for the difference in estimated standardized mortality ratios.

Cushing's syndrome is a fatal condition in the absence of adequate treatment (27). Recent studies have reported SMR in treated patients with Cushing's disease ranging from 1.0 to 3.8 (9;10;28;29). However, confidence intervals in these studies were broad. In the present study mortality in patients treated for Cushing's disease was 2.4 fold increased compared with the general population. Moreover, mortality risk after transsphenoidal surgery for Cushing's disease was also increased compared with NFMA patients, who were treated identically. This points towards effects of previous exposure to cortisol excess on mortality risk in patients with Cushing's disease. The importance of cortisol in mortality excess is further underscored by the fact that mortality is increased in patients with persistent Cushing's disease after treatment, compared with cured patients (28;30). This indicates that the duration of exposure to overproduction of cortisol is a major contributor to the increased mortality risk observed in Cushing's disease. Cortisol excess induces central obesity, diabetes mellitus, hyperlipidemia and hypertension (2). There is evidence that the increased cardiovascular risk in Cushing's disease continues even after remission of the disease (3;4). Therefore, the effects of transient cortisol overproduction may not be reversible with respect to certain biological properties that influence mortality.

In order to further evaluate our conclusion that cortisol excess is responsible for the increased mortality in Cushing's disease, we also compared mortality in Cushing's disease to mortality in patients with acromegaly. These mortality data from our center in patients with acromegaly after transsphenoidal surgery have been published previously (22). Compared with acromegaly the mortality risk, adjusted for sex and age, in patients with Cushing's disease was 2.4 fold increased (95% CI 1.13-4.91) (See Figure 1). This indicates that the increased mortality in patients with Cushing's disease is not due to hormonal overproduction in general, but due to intrinsic properties of the exposure to cortisol excess.

In conclusion, this study demonstrates that mortality in patients after transsphenoidal surgery for pituitary tumors is increased. Moreover, the relative mortality risk is increased in patients with Cushing's disease compared with both NFMA and acromegaly. This implicates that transient exposure to cortisol excess is a major contributor of the increased mortality, even after cure of Cushing's disease. This observation may also be of relevance for patients treated with exogenous glucocorticoids for non-endocrine diseases.

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Quality of life is decreased in patients treated for nonfunctioning pituitary macroadenoma

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CHAPTER 6

SUMMARY

Objective. Although a reduced quality of life (QoL) has been reported after long-term cure of functioning pituitary adenomas, the effect of successful treatment of nonfunctioning pituitary macroadenoma (NFMA) on QoL has not been fully addressed. Therefore, we evaluated a broad spectrum of QoL parameters in patients successfully treated for NFMA in our center.

Design. Case-control study.

Patients and Methods. We assessed QoL in 99 adult patients (mean age 61.9, range 24-86 yr), in remission during long-term follow up after surgical (n=99) and additional radiotherapeutic (n=37) treatment for NFMA by four validated health-related questionnaires (HADS, MFI-20, NHP, SF-36). Patient outcomes were compared with 125 controls and with age-adjusted reference values derived from literature.

Results. NFMA patients reported significantly impaired QoL in all questionnaires, compared with the 125 controls and the age-adjusted reference values. All subscales of fatigue, assessed using the multi-dimensional Fatigue Index (general fatigue, physical fatigue, reduction in activity, reduction in motivation, mental fatigue) were impaired. The scores in the Nottingham Health Profile pointed towards reduced energy and affected emotional reaction. In several subscales of the Short Form-36 (social functioning, role limitations due to physical problems, role limitations due to emotional problems and general health perception) NFMA patients reported a reduced QoL.

Conclusion Quality of Life is considerably reduced in patients after successful treatment of NFMA.

INTRODUCTION

Nonfunctioning pituitary macroadenomas (NFMA) are the most prevalent pituitary macroadenomas (1;2). The main symptoms are visual field defects and hypopituitarism, which are caused by mass effects of the tumor. Transsphenoidal surgery is considered the treatment of choice, because medical therapy in general is ineffective to reduce tumor size. Visual field defects improve in more than 80% of all patients after surgery (3-6). In contrast, hypopituitarism does not improve in most patients after surgery for NFMA (5;7-9). To prevent tumor recurrence, selected patients may be treated by postoperative radiotherapy (10).

In general, pituitary diseases are associated with impaired quality of life (QoL) (11). This can be explained by several factors. Macroadenomas are associated with different degrees of hypopituitarism, which require hormonal substitution. However, despite optimal endocrine replacement strategies, hypopituitarism is associated with impaired QoL parameters (12;13). Moreover, Growth hormone (GH) and ACTH producing adenomas may induce irreversible effects, which persist despite long-term cure of the disease (12;13). Finally, an association between applied radiotherapy and decreased QoL has been reported (12;14).

Most studies on QoL in pituitary diseases were not focussed on NFMA, but included heterogeneous groups, consisting of both functioning and nonfunctioning pituitary tumors (11;15-17). To our knowledge, no studies on QoL in patients treated for NFMA, compared with healthy controls, have been published. Therefore, in the present study the aim was to assess QoL in adult NFMA patients treated by transsphenoidal surgery. Patient outcomes of QoL parameters were compared with those of control subjects as well as to age-adjusted reference values derived from literature. We evaluated physical, psychological, and social aspects of QoL in patients after long-term cure, using four validated, health-related QoL-questionnaires covering a broad spectrum of physical, psychological and social health: HADS, MFI-20, SF-36 and NHP.

PATIENT AND METHODS.

Protocol

A total of 128 consecutive patients with NFMA, treated by transsphenoidal surgery in our center between 1985 and 2004, were identified. QoL questionnaires were sent to their homes in prepaid envelopes. After three months non-responders were contacted by telephone to encourage completion and return of the questionnaires. Each patient was also asked to provide a control person of comparable age and sex to serve as a control group with a comparable socio-economic status derived from the same geographical area. In addition to this control group, we used reference data from healthy subjects of the Dutch and west European population, obtained from studies reporting normal age-adjusted values (18-22).

All patients were seen at least twice yearly by an endocrinologist, with adequate evaluation and treatment of possible deficiencies of pituitary hormones. Evaluation of ACTH deficiency and GH deficiency was performed by insulin-tolerance test. Previous studies have demonstrated that patients with multiple pituitary hormone deficiencies, including two or more pituitary hormone deficiencies other than GH deficiency, had a likelihood of approximately 95% of harbouring GH deficiency (23-25). Based on these data, we classified patients in whom GH-stimulation test data were lacking, but who were deficient in 3 other pituitary axes, as GH deficient. In addition, the biannual evaluation consisted of measurement of free T_4 and testosterone (male patients). If results were below the lower limit of the respective reference ranges, substitution with thyroxine or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

The medical ethics committee of the Leiden University Medical Centre approved the study protocol.

Patients and controls (Table 1)

One-hundred-and-sixteen of 128 (91%) patients returned the questionnaires, 17 of whom preferred not to participate. Twelve patients did not respond. Thus, 99 completed questionnaires were received (77%). The study-population had a mean age of 61.9 yr, (range 24-86 yr). No significant differences in age, gender and tumor characteristics were found between the study-population, and the patients who preferred not to participate or who did not return the questionnaires.

Sixty-six controls were provided by the 99 patients who returned the questionnaires (67%). The control group was extended by controls derived from other studies in our center, who had been similarly approached (12;13). The total control group consisted of 125 controls (66 males, 59 females), with a mean age of 61.5 yr, range 26-86 yr. Age and gender from the control group were not significantly different from the studied NFMA patients.

Study parameters

Primary study-parameters were the results of the four health-related QoL questionnaires. The results were linked to characteristics (age and gender) of the patients, treatment characteristics (surgery, radiotherapy, and multiple surgical procedures), the presence of pituitary deficiencies and visual field defects.

Questionnaires

HADS (Hospital Anxiety and Depression Scale) The HADS consists of 14 items pertaining to anxiety and depression. Each item is measured on a four-point scale. Scores for the anxiety and depression subscale range from 0-21 and for the total score from 0-42. A high score points to more severe anxiety and depression (26). A total score of 13 or more was considered increased. Age-related Dutch reference values of the general population were derived from the study of Spinhoven *et al.* (20).

MFI-20 (Multidimensional Fatigue Index) The MFI-20 contains 20 statements to assess fatigue (27). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. Every statement is measured on a 5-point scale; scores vary from 0 to 20. Higher scores indicate higher experienced fatigue. Age-related Dutch reference values were derived from Smets *et al.* (19).

NHP (Nottingham Health Profile) The NHP is frequently used in patients with pituitary disease to assess general well-being and QoL. The survey consists of 38 yes/no questions, which are subdivided in 6 scales assessing impairments, i.e. pain (8 items), energy level (3 items), sleep (5 items), emotional reactions (9 items), social isolation (5 items) and disability/functioning, *i.e.* physical mobility (8 items) (28;29). Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the 6 subscales. A high score is related to a worse QoL. Age-related West-European reference values were derived from the study from Hinz *et al.* (18).

SF-36 (Short Form-36) The SF-36 questionnaire comprises 36 items and records general well being during the previous 30 days (30;31). The items are formulated as statements or questions to assess eight health concepts: 1) physical functioning, 2) social functioning, 3) limitations in usual role activities because of physical health problems, 4) pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions and change in health. Because the HADS and the MFI-20 are more specific questionnaires for mental health and fatigue, the vitality and general mental health items were left out in this evaluation. Because the scores for the 8 items are calculated separately from exclusive item-specific questions (21), the results of the SF-36 items presented in this study are not influenced by the 2 items we left out in this evaluation. Scores are expressed on a 0-100 scale. Higher scores are associated with better QoL. Age-related West-European reference values were derived from the Dutch manual (21;22).

Statistics

SPSS for windows version 12.0 (SPSS Inc., Chicago, IL) was used for data analysis. Data are expressed as mean ± SD, unless otherwise mentioned. We used unpaired T-tests to compare patient and control data. Using stepwise linear regression analysis we assessed independent variables that affect QoL. Results of the linear regression analysis are expressed as the absolute standardized β of independent predictive factors. One-way ANOVA analysis was performed to compare QoL scores of three different groups: Patients without GH deficiency, patients with GH deficiency, substituted with recombinant human (rh)GH and patients with GH deficiency without rhGh substitution). Differences were considered statistically significant at P <0.05.

RESULTS

Patient and treatment characteristics (Table 1)

Patient characteristics are detailed in Table 1. All 99 patients had been treated by trans-sphenoidal surgery. Twenty-two patients had received prophylactic postoperative radiotherapy. Repeat surgery within 6 months after initial treatment was performed in 8 patients for a large residual tumor mass (n=4), persisting liquor leakage (n=3) or profuse bleeding (n=1). The mean follow-up period after initial surgical treatment was 9.9 ± 6.6 yr. In 17 patients tumor recurrence was observed by MRI scanning, after a mean follow-up duration of 7.1 ± 4.0 yr. Tumor recurrence was treated by radiotherapy (n=11), or a combination of surgery and radiotherapy (n=4). In the remaining 2 patients an expectant approach was undertaken.

At the time of evaluation, 83% of the patients were GH deficient, 82% were LH/FSH deficient, 63% were ACTH deficient and 62% were TSH deficient. Hypopituitarism, defined as pituitary deficiency in at least one axis, was present in 93 of 99 patients, panhypopituitarism of the anterior pituitary gland in 48%. Diabetes insipidus was present in 9% of the patients. All patients with ACTH and TSH deficiency received hormonal substitution therapy. Of all GH deficient patients, 42 (51%) received rhGh substitution at the time of evaluation. Of all GH deficient patients without substitution at time of evaluation, rhGH was stopped in 8 cases.

Finally, visual field defects were present in 41% of cases.

Quality of Life in NFMA-patients compared with controls and age-adjusted reference-values (Table2):

NFMA patients reported an impaired QoL compared with the 119 controls and the age-adjusted reference values. The QoL scores were significantly reduced in 19 out of 21 subscales as compared with own controls, and in 10 out of 21 subscales as compared with age adjusted reference values.

Table 1. Characteristics of NFMA patients and controls

	NFMA Patients (N=99)	Controls (N=125)
Age (yr)	61.9, range 24-86	61.5, range 26-86
Sex (M/F)	54/45	66/59
Age at diagnosis	50.7±11.7	
Pituitary function		
GH deficiency	83%	
Mean IGF-I SD score in rhGH substituted patients	1.0 ± 1.9	
Mean IFG-I SD score in GH deficient, non-substituted patients	-1.6 ± 1.9	
LH/FSH deficiency	82%	
ACTH deficiency	63%	
Mean daily dose of hydrocortisone (mg) in substituted patients	20.3 ± 4.3	
TSH deficiency	62%	
Mean free T4 levels (pmol/L) in substituted patients (normal 10.0-24.0)	17.9 ± 3.5	
Any degree of hypopituitarism	93%	
Two or more pituitary deficiencies	80%	
Panhypopituitarism of the anterior pituitary gland	48%	
Diabetes insipidus	9%	
General medical illness and disability		
Visual field defects	41%	
Diabetes Mellitus	13%	
Cardiovascular disease	7%	
Joint complaints	53%	

Compared with own controls, in patients with NFMA, all subscales of the MFI-20, assessing different aspects of energy/fatigue, were affected. The majority of items assessed by the SF-36 and the NHP, two questionnaires covering multiple aspects of general health and well-being, were affected (with the exception of pain (NHP and SF-36) and health change (SF-36)). On the 3 subscales of the HADS, NFMA patients performed worse compared with own controls.

Compared with age-adjusted reference values, the majority of subscales of the MFI-20 were affected, with the exception of general fatigue. According to the SF-36 scores of 4 out of 7 subscales were reduced (social functioning, role limitations due physical, emotional problems and general health perception). Only two subscales of the NHP (energy and emotional reaction) pointed toward a reduced QoL in NFMA patients. There was no significantly affected QoL parameter according to the HADS questionnaire, compared with age adjusted reference values.

The effect of GH deficiency and GH replacement on QoL

A substantial proportion (49%) of the NFMA patients with GH deficiency were not substituted with rhGH. To assess the effect of GH deficiency and rhGH replacement on QoL, we performed ANOVA analysis comparing three groups: patients without GH deficiency (n=16), patients with GH deficiency, substituted with rhGH (n=42) and patients with GH deficiency, but without rhGh substitution (n=41). The only significant difference between

Table 2. Quality of Life parameters (HADS, MFI-20, NHP, SF-36) in treated NFA patients compared with controls and age-adjusted reference values

	NFA patients (n = 99)	Controls (n = 125)	p-value[1]	Age-adjusted reference values [2]	p-value[3]
HADS					
Anxiety	5.00±3.77	3.80±3.18	=0.01	5.04±3.64	ns
Depression	4.39±4.44	3.12±2.63	<0.01	3.79±3.42	ns
Total	9.39±7.49	6.90±5.10	<0.01	8.41±6.31	ns
MFI-20					
General fatigue	11.26±5.48	8.00±3.82	<0.001	9.92±5.18	ns
Physical fatigue	10.68±5.08	7.86±3.72	<0.001	8.79±4.91	<0.01
Reduction in activity	10.19±5.12	7.30±3.40	<0.001	8.68±4.62	<0.05
Reduction in motivation	9.58±5.01	7.71±3.61	<0.01	8.24±4.03	<0.05
Mental Fatigue	9.83±5.04	7.41±3.78	<0.001	8.26±4.79	<0.05
NHP					
Energy	27.48±39.59	4.53±16.26	<0.001	15.81±25.54	<0.01
Pain	10.24±22.36	5.20±14.29	ns	10.72±18.42	ns
Emotional reaction	15.24±23.01	4.37±13.00	<0.001	9.01±16.21	<0.05
Sleep	18.04±26.77	9.22±19.59	<0.05	18.94±25,01	ns
Physical mobility	10.28±19.11	4.76±11.45	<0.01	9.48±13.93	ns
Social isolation	10.54±22.17	1.02±5.29	<0.001	5.83±16.02	ns
SF-36					
Physical functioning	79.04±22.65	86.37±17.30	<0.01	71.69±25.24	ns
Social functioning	78.97±22.92	93.66±12.39	<0.001	85.12±22.38	<0.05
Role limitations due to physical problems	65.00±40.18	86.99±27.41	<0.001	73.66±39.14	<0.05
Role limitations due to emotional problems	69.07±39.75	89.46±24.60	<0.001	84.43±31.36	<0.001
Pain	81.28±20.72	86.58±17.95	ns	76.30±26.55	ns
General health perception	57.32±24.25	70.33±15.63	<0.001	64.93±22.49	<0.05
Health change	50.26±22.92	51.82±16.05	ns	48.94±18.04	ns

[1] patients compared with own controls.

[2] derived from references 18-22.

[3] patients compared with literature reference data

these three groups was in sleep performance (NHP, $P < 0.05$). Sleep was most affected in patients with a GH deficiency, substituted with rhGH.

Linear regression

Stepwise uni-variate linear regression analysis was performed in a model including: gender, age, radiotherapy, multiple operations, ACTH-deficiency, TSH deficiency, LH/FSH deficiency, GH deficiency, multiple pituitary deficiencies and visual defects as independent variables, and the questionnaire items as dependent variables.

Age was an independent predictor for reduced physical ability (NHP, standardized β = 0.48, $P<0.01$) and reduced physical function (SF-36, standardized β = 0.48, $P < 0.01$). The presence of multiple hormonal deficiencies was an independent predictor for role limitations due to physical problems (SF-36, standardized β = 0.28, $P < 0.05$), impaired social functioning (SF-36, standardized β = 0.29, $P < 0.05$) and sleep (NHP, standardized β = 0.25, $P < 0.05$) and increased general fatigue (MFI-20, standardized β = 0.24, $P< 0.05$). LH/

FSH deficiency was an independent predictor for reduced activity (MFI-20, standardized $\beta = 0.28$, $P < 0.05$) and increased physical fatigue (MFI-20, standardized $\beta = 0.25$, $P < 0.05$). Female gender was an independent predictor for increased anxiety (HADS, standardized $\beta = 0.35$, $p < 0.05$). Radiotherapy, visual field defects and GH deficiency were not found to be independent predictors for reduced QoL in any of the questionnaires.

DISCUSSION

The data in this study indicate that quality of life is reduced in patients successfully treated for NFMA. According to the parameters tested by the HADS, MFI-20, NHP and SF-36 questionnaires, patients reported a decreased QoL in 10 out of 21 subscales, compared with both age-adjusted reference values and controls. Almost all subscales of the MFI-20, assessing energy/fatigue, showed a significant decreased QoL. Linear regression analysis revealed the presence of multiple pituitary deficiencies, and, to a lesser extent age, as the predominant predictors of a decreased QoL.

In the present study, NFMA patients were compared with own controls and age-adjusted reference values derived from literature. The advantage of using own controls is that they are from the same geographic area and socio-economic class as the patients (32). However, these controls might be subject to a selection bias, because patients might have chosen controls with a supposed good health status (33). To overcome this potential bias, we also compared the NFMA patients to age-adjusted reference values from the literature. Moreover, the use of two different control groups might lead to more credible results if the results are consistent (32). The scores of the NFMA patients showed an impaired QoL in more subscales of the four questionnaires, compared with own controls than compared with the age-adjusted reference-values, confirming the possible difference in health status between the two groups. Nonetheless, even compared with the reference data obtained from the literature, our NFMA patients scored worse, supporting our conclusions with respect to the negative effect of NFMA on QoL. Although the response rate in our series of patients with NFMA was 91%, and completed questionnaires were received of 77% of the patients, it seems unlikely, that the non-responders have influenced the outcome of our study, because there were no differences in patient characteristics between responders and non-responders/decliners.

Literature on QoL in patients with NFMA is scarce. To our knowledge only two studies evaluated QoL in NFMA patients (11;14). Johnson *et al.* reported a reduced QoL in NFMA patients, before treatment, using the SF-36 questionnaire, compared with scores from the normal population (11). Other reports on QoL in NFMA, consisting of heterogeneous groups of patients with both functioning and nonfunctioning tumors, showed a reduced QoL in patients with pituitary tumors in general (15;34;35). However, it was not possible

Table 3. Summary of SF-36 results in patients treated for nonfunctioning pituitary macroadenomas and in patients after mastoid surgery

	NFA treated (own data)	Mastoid surgery (14)
Mean age (yr)	62	61
Physical functioning	79 ± 23	71 ± 31
Physical role	65 ± 40	74 ± 40
Emotional role	69 ± 40	83 ± 35
Social functioning	79 ± 23	83 ± 26
Bodily pain	81 ± 21	76 ± 25
Health perception	57 ± 24	68 ± 21

to perform subgroup analysis in order to estimate QoL specifically in NFMA, because of the small number of patients (15;34). Moreover, the effects of pituitary diseases on QoL cannot simply be generalized for all pituitary diseases. NFMA patients differ from patients with functioning pituitary adenomas in several aspects. NFMA is more prevalent in older and male patients compared with functioning pituitary adenomas (36). Nonfunctioning adenomas are treated only when tumor size indicates a macroadenoma, whereas treatment indication in functioning adenomas is focused at hormone overproduction in addition to tumor size. Therefore, pituitary tumors in treated NFMA tend to be larger than tumors in patients treated for functioning pituitary adenomas. In accordance, in NFMA patients there is a higher degree of pituitary deficiencies, whereas patients cured from functioning pituitary tumors also suffer from irreversible effects of previous hormone overproduction, as is the case in functioning adenomas such as Cushing's disease or acromegaly (12;13). Compared with NFMA, QoL in acromegaly patients is clearly decreased (17). QoL-assessment in heterogeneous groups, consisting of both functioning and nonfunctioning adenomas, may therefore not be an appropriate strategy to assess QoL in patients treated for NFMA.

The study from Page *et al.* did not reveal a reduced QoL in surgically treated NFMA patients, compared with patients after mastoid surgery (14). The results of the SF-36 questionnaire from these patients after mastoid surgery are summarized in Table 3. These results do not show concordant differences compared with our NFMA patients, pointing toward a general role for medical illness in impaired QoL. However, this also underscores the notion that the SF-36 questionnaire is not disease-specific, *i.e.* is not specific for the assessment of QoL in patients with pituitary diseases.

Our results point toward a reduced QoL in physical and psychological as well social items. Treated NFMA patients report increased fatigue, both mental and physical, reduced energy and role limitations due to physical problems as well as reduced activity and reduced motivation. Interestingly, physical functioning seemed not to be affected compared with age adjusted reference values. NFMA patients also report affected emotional reactions, role limitations due to emotional problems as well as affected social functioning.

Nonetheless, the HADS questionnaire did not reveal any significant difference between NFMA patients and age-adjusted reference values. This finding is in accordance with the report of Korali *et al.* in which no elevated rates of mental disorders could be found after treatment for NFMA, even in the case of multiple pituitary deficiencies (37).

We could not properly assess the effect of hypopituitarism *per se* on QoL, because hypopituitarism was present in 93% of all NFMA patients. Although the number of patients with hypopituitarism seems rather high, it is comparable to the percentage (94%) of patients with hypopituitarism presented in a series of consecutive patients treated for NFMA in our hospital (38). The patient population in the present series seems therefore not skewed towards those patients with more severe disease. Hypopituitarism was found to be an independent predictor of reduced QoL in patients treated for Cushing's disease, affecting both physical and psychosocial items (13). In the present study, the presence of multiple pituitary deficiencies was the most predominant predictor for decreased QoL, pointing toward an important role of pituitary function for optimal QoL. Hormonal substitution therapy does not reproduce the normal plasma hormone profiles of healthy individuals. Moreover, the effects of hormones in general are difficult to quantify at the tissue level. Consequently, titration of endocrine replacement therapy is possible only within certain physiological limits. These intrinsic imperfections in endocrine replacement therapy may result in subtle physiological derangements. Most importantly, this imperfection in endocrine substitution may result in a decreased QoL. In this study LH/FSH deficiency was an independent predictor for reduced activity and increased physical fatigue. This may reflect the lack of sensitive signs and symptoms for monitoring adequacy of testosterone and estrogen substitution (39). We did not measure routinely levels of dehydroepiandrostenedione (DHEA). However, we recently documented in a randomized placebo-controlled trial, that DHEA substitution superimposed on GH-substitution did not substantially improve QoL in patients with secondary adrenal failure (40). In this study, female gender was an independent predictor for anxiety. The predisposition for female gender as an independent risk factor for a decreased QoL is unclear, and has been previously described in patients with primary brain tumors (41). However, it does not seem to be a disease specific phenomenon given the fact that QoL studies in nonpituitary diseases (malignancies, coronary heart disease, inflammatory bowel disease) also report decreased QoL in female patients as compared with male patients (41-45).

GH deficiency was not found to be an independent predictor for any of subscales of the four questionnaires. In our study only 51% of all GH deficient patients received rhGH substitution. We could not detect a beneficial effect of rhGH substitution on QoL scores. However, this study was, in strict sense, not designed to assess the effect of rhGH substitution on QoL. A recent meta-analysis on the effect of rhGh substitution on various QoL subscales, suggested that rhGH substitution does not improve QoL compared with placebo (46). Moreover, several studies report an improved QoL and well-being (47-50), suggesting that in selected patients rhGH substitution may have a beneficial effect on QoL (51).

The four health-related questionnaires used in this study, were not disease-specific, *i.e.* they were not developed to assess QoL in NFMA, although the NHP is frequently used in patients with pituitary disease. However, we found a reduced QoL in the majority of subscales of the MFI-20, the SF-36 and the NHP. This seems to point toward a strong overall effect of the pituitary diseases on general health and well being of both the physical and the psychosocial aspects.

In conclusion, Quality of Life is reduced in patients after successful treatment of NFMA. According to the MFI-20, NHP and SF-36, patients reported a decreased QoL in almost all subscales compared with age-adjusted reference values and controls. The presence of multiple pituitary deficiencies was the predominant predictor for a reduced QoL.

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Quality of life in treated adult craniopharyngioma patients

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CHAPTER 7

SUMMARY

Objective. Quality of Life (QoL) has become increasingly important in the evaluation of treatment of pituitary and hormonal diseases. A reduced QoL has been reported in childhood onset craniopharyngioma; however, reports of QoL in adult craniopharyngioma patients are scarce. In the present study, we assessed QoL in adult patients successfully treated for craniopharyngioma in our centre.

Design. Case-control study.

Methods. In this study we assessed QoL in 29 adult patients in remission during long-term follow-up after treatment for craniopharyngioma. Four validated health-related questionnaires (HADS, MFI-20, NHP, SF-36) were used, covering multiple aspects of physical, psychological and social functioning. Patient outcomes were compared to controls (n=142) and to age adjusted reference values derived from literature.

Results. General fatigue, physical fatigue, energy, physical condition and physical mobility were significantly impaired, compared to controls. The main independent predictors for a decreased QoL were visual field defects (depression, total HADS score, activity, motivation and energy), female gender (depression, motivation and pain), and, to a lesser extent, repeat surgery (role limitations due to emotional problems), and radiotherapy (mental fatigue).

Conclusion. Adult patients treated for craniopharyngioma show persistent impairment in Quality of Life, especially in the physical subscales.

INTRODUCTION

Craniopharyngiomas are histologically benign brain tumours arising from the remnants of Rathke's pouch. Despite their benign appearance, their clinical behaviour is aggressive, causing serious morbidity by damaging the optic chiasm, the pituitary, and hypothalamic area. Currently, craniopharyngioma is treated primarily by transsphenoidal or transcranial surgery, whereas post-surgical radiotherapy is not routinely applied in all patients (1;2). Recurrent disease is treated by repeat surgery and/or radiotherapy.

In adults, treatment of craniopharyngioma is associated with excessive multi-system morbidity and increased mortality during long-term follow-up despite a high cure rate (3-6). There is a high incidence of pituitary insufficiencies, and visual field defects may persist in some patients (1-4). Finally, there is a high incidence of cardiovascular risk factors in these patients (1;3;4).

Pituitary diseases in general are associated with decreased quality of life (QoL) and cognitive dysfunction, despite optimal replacement strategies for pituitary insufficiency, and long-term cure of hormone excess syndromes such as Cushing's disease and acromegaly (7-10). Hypopituitarism and radiotherapy are important factors for impaired QoL. Reduced QoL has been reported in childhood onset craniopharyngioma (3;11-13). To our knowledge, QoL in adult craniopharyngioma patients has been reported in only one study (3). In this study, QoL was markedly reduced, as assessed by two questionnaires (NHP and QoL-AGHDA), the latter being a disease specific questionnaire, designed to assess physical and psychological discomfort in adult growth hormone deficiency. Given the high prevalence of associated morbidity found in our adult craniopharyngioma patients (4), we wanted to extend these observations by assessment of QoL in more detail.

In the present study we assessed QoL in adult patients successfully treated for craniopharyngioma in our centre. We evaluated physical, psychological, and social aspects of QoL in patients after long-term cure, using four validated, health-related QoL-questionnaires. Patient outcomes were compared with own control values as well as to age-adjusted reference values derived from literature.

PATIENTS AND METHODS

Protocol

Forty-three patients treated and cured for craniopharyngioma, followed in our centre from 1965 to 2002, were identified. Four QoL-questionnaires were sent to their homes. They were asked to participate and to complete, and return the questionnaires in a prepaid envelope. Non-responders received a reminder letter. Thereafter, they were contacted once by telephone and encouraged to complete and return the questionnaires.

Patients were also asked to provide a control person with comparable age and sex (for example a relative – not the partner –, friend or neighbour) in order to compose a control population with similar socio-economic status derived from the same geographical area. In addition to this control group, we used literature reference data from healthy samples of the Dutch and west European population from studies reporting normal age-adjusted values (14-18). These data are based on larger study populations than our own controls and are therefore not affected by a potential positive selection by the patients.

The medical ethics committee of the Leiden University Medical Centre approved the study protocol.

Patients and controls (Table 1)

Thirty-three of 43 (77%) patients returned the questionnaires, four of whom preferred not to participate. Thus, 29 completed questionnaires were received. The study population of 29 patients (15 males) had a mean age was 47.9 ± 17.6 years (range 11-80 yr). All patients were primarily treated by surgery. Nine patients received radiotherapy, four of whom for recurrence. Seven patients had repeat surgery. Mean follow-up after primary surgery was 19.9 ± 13.1 years and all patients were cured of disease. Hypopituitarism was present in 93% of cases. No significant differences in age, gender and tumour characteristics were found between the study population and the patients who did not return the questionnaires.

Twenty-five controls returned completed questionnaires. The control group was extended by controls derived from other studies performed at our centre, who had been similarly approached (7;9). Therefore, the total control group consisted of 142 controls (88 females, 54 males), with a mean age of 53.8 ± 14.5 yr. No significant differences in QoL measures were present between the three control groups, justifying their combined use. Age and gender were not significantly different from the studied craniopharyngioma patients.

Study parameters

Primary study-parameters were the results of four health-related QoL questionnaires. The results were linked to patient characteristics (age and sex), applied treatments (surgery, radiotherapy and multiple surgical procedures), presence of hypopituitarism and visual impairments. Hypopituitarism was defined as one or more pituitary hormone deficiencies.

Questionnaires

HADS (Hospital Anxiety and Depression Scale) The HADS consists of 14 items pertaining to anxiety and depression. Each item is measured on a 4-point scale. The range of scores for the anxiety and depression subscale is 0-21 for the total score 0-42. A high score points to more severe anxiety and depression (19). Age-related Dutch reference values of the general population were derived from the study of Spinhoven *et al.* (16).

MFI-20 (Multidimensional Fatigue Index) The MFI-20 contains 20 statements to assess fatigue (20). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation and 5) mental fatigue. Every statement is measured on a 5-point scale; scores range from 0 to 20. Higher scores indicate higher experienced fatigue. Age-related Dutch reference values were derived from Smets *et al.* (15).

NHP (Nottingham Health Profile) The NHP is frequently used in patients with pituitary disease to assess general well-being and QoL. The survey consists of 38 yes/no questions, subdivided into the following 6 scales assessing impairments: 1) pain (8 items), 2) energy level (3 items), 3) sleep (5 items), 4) emotional reactions (9 items), 5) social isolation, (5 items), and 6) disability/functioning, i.e. physical ability (8 items) (21;22). Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the 6 subscales. Higher scores are related to worse QoL. Age-related west-European reference values were derived from the study from Hinz *et al.* (14).

SF-36 (Short Form-36) The SF-36 questionnaire comprises 36 items and records general well being during the previous 30 days (23;24). The items are formulated as statements or questions to assess eight health concepts: 1) physical functioning, 2) social functioning, 3) limitations in usual role activities because of physical health problems, 4) pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions and change in health. Because the HADS and the MFI-20 are more specific questionnaires for mental health and fatigue, the vitality and general mental health items were left out in this evaluation. Scores are expressed on a 0-100 scale. Higher scores are associated with better QoL. Age-related west-European reference values were derived from the Dutch publications of Van Zee *et al.* (17;18).

Statistics

SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL) was used to perform data analysis. Data are expressed as mean ± SD unless otherwise mentioned. We used unpaired T-tests to compare patient and control data. Using linear regression analysis, we assessed independent variables that affect quality of life. Differences were considered statistically significant at $p = 0.05$ or less.

Table 1. Characteristics of the craniopharyngioma patients and controls.

	Craniopharyngioma patients *(n=29)*	Controls *(n=142)*
Age (years)	47.9 ± 17.6	53.8 ± 14.5 (P = NS)
Male/Female	15/14	88/54 (P = NS)
Age at diagnosis (years)	27.9 ± 16.2	
Childhood onset	8 (28%)	
Radiotherapy	9 (31%)	
Repeat surgery	7 (24%)	
Persistent visual field defects	12 (41%)	
Intact pituitary function	2 (7%)	
Single pituitary deficiency	0	
Multiple pituitary deficiencies*	5 (17%)	
Panhypopituitarism**	22 (76%)	

NS denotes not significant.

* Defined as pituitary deficiency in more than 1 axis

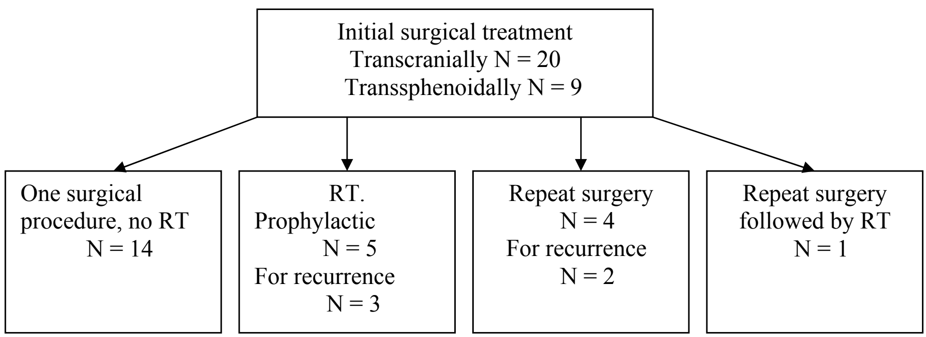
** Defined as pituitary deficiency in all four axes

RESULTS

Patient characteristics (Table 1 and Figure 1)

Clinical characteristics are detailed in Table 1. Primary surgery was performed in all 29 patients. Nine (31%) patients received radiotherapy after primary surgery, and seven patients (24%) needed more than one operation. The different treatment modalities are summarized in Figure 1. At the time of evaluation in two patients pituitary function was intact. These two patients were both reoperated because of tumor regrowth and suffered both from visual field defects. Five (17%) patients had pituitary deficiency in 3 of 4 axes. In the majority of patients (76%), panhypopituitarism was present. Twelve (41%) patients had persistent visual impairments.

Figure 1. Patient groups, stratified according to different treatment modalities.



RT denotes radiotherapy.

Quality of Life in craniopharyngioma patients and controls (Table 2)

Compared to the 142 controls and the age-adjusted reference values, the craniopharyngioma patients had reduced QoL in every questionnaire, except for the HADS. According to the HADS there was no significant difference between patients and controls in items concerning anxiety and depression. All subscales of fatigue assessed by the MFI-20 were affected, especially general and physical fatigue. Reduction in activity and motivation did not reach statistical significance when compared with the age-adjusted reference values. The scores of the patients on the NHP pointed to reduced energy and physical mobility. Sleep, emotional reaction and social isolation scores were not significantly different from the controls. Health perception, as assessed by the SF-36, was significantly affected in craniopharyngioma patients. Moreover, physical and social functioning was reduced, as compared with own controls.

Factors affecting Quality of Life in craniopharyngioma patients

Childhood- versus adult-onset craniopharyngioma. Adult-onset craniopharyngioma patients performed worse on the depression score (HADS, $P < 0.05$) than childhood-onset patients.

Gender. Compared with males, females reported a decreased QoL for several energy-related items, such as general fatigue (MFI-20, $P < 0.01$), reduced motivation (MFI-20, $P < 0.05$) and energy (NHP, $P < 0.01$), and also for pain (NHP, $P < 0.05$), social functioning (SF-36, $P < 0.05$) and role limitations due to physical problems (SF-36, $P < 0.05$).

Age. Younger patients were more affected on the following subscales: social isolation (NHP, $P < 0.05$) and social functioning (SF-36, $P < 0.05$). No age-related differences were found on items concerning energy and physical functioning.

Radiotherapy. Only mental fatigue was significantly affected in patients treated by radiotherapy (MFI-20, $P < 0.01$).

Repeat surgery. Patients who underwent multiple operations performed worse on general fatigue (MFI-20, $P < 0.05$), sleep (NHP, $P < 0.05$) and health change (SF-36, $P < 0.01$).

Visual field defects. The presence of persistent visual field defects significantly affected the following items: total HADS score ($P < 0.05$), general fatigue (MFI-20, $P < 0.05$), reduced activity (MFI-20, $P < 0.01$), reduced motivation (MFI-20, $P < 0.01$), energy (NHP, $P < 0.01$), social functioning (SF-36, $P < 0.05$) and role limitations due to physical problems (SF-36, $P < 0.05$).

Multiple pituitary deficiencies/panhypopituitarism. Scores from patients with intact pituitary function (n=2) indicated more reduced QoL in all subscales of the HADS and the MFI-20, as compared with patients with multiple pituitary deficiencies/panhypopituitarism. However, the SF-36 scores from patients with multiple pituitary deficiencies/pan-

Table 2. Quality of Life (HADS, MFI-20, NHP, SF-36) in treated craniopharyngioma patients compared to controls and age-adjusted reference values

	Craniopharyngioma patients (n = 29)	Controls (n = 142)	p-value [a]	Age-adjusted reference values [b]	p-value [c]
HADS					
Anxiety	3.59±3.15	4.02±3.21	ns	4.89±3.60	ns
Depression	3.31±3.01	3.33±3.02	ns	3.61±3.35	ns
Total	6.90±5.41	7.35±5.43	ns	8.42±6.32	ns
MFI-20					
General fatigue	11.76±4.20	8.33±3.76	<0.001	9.91±5.20	<0.025
Physical fatigue	11.57±4.33	7.87±3.89	<0.001	8.79±4.90	<0.005
Reduction in activity	9.69±4.10	7.39±3.45	<0.01	8.69±4.60	ns
Reduction in motivation	9.61±4.11	7.73±3.83	<0.05	8.23±4.00	ns
Mental Fatigue	9.62±4.66	8.00±4.10	<0.1	8.33±4.80	ns
NHP					
Energy	20.11±28.63	5.55±18.01	<0.001	10.34±25.5	<0.05
Pain	9.42±19.91	5.54±14.38	ns	6.17±18.4	ns
Emotional reaction	9.11±18.56	5.47±15.33	ns	7.31±16.2	ns
Sleep	12.08±16.65	9.18±22.21	ns	12.86±25	ns
Physical ability	11.43±19.15	5.68±12.97	<0.05	4.69±13.9	0.05
Social isolation	6.57±18.77	1.67±7.74	<0.05	5.38±16	ns
NHP total score	11.41±13.73	5.31±10.42	<0.01	[d]	
SF-36					
Physical functioning	72.24±24.30	85.92±19.42	<0.001	79.16±21.59	ns
Social functioning	83.62±19.79	90.96±17.04	<0.05	86.28±20.77	ns
Role limitations due to physical problems	79.46±28.91	87.86±27.56	ns	77.66±36.24	ns
Role limitations due to emotional problems	94.05±20.39	88.57±28.21	ns	83.73±32.31	ns
Pain	80.51±16.88	85.83±19.14	ns	79.70±25.05	ns
General health perception	54.82±26.19	72.02±17.79	<0.01	69.43±21.89	<0.005
Health change	50.86±21.63	56.91±18.69	ns	51.44±18.54	ns

Data shown are the mean ± SD

[a] Patients compared with own controls by the unpaired two-tailed t-test

[b] Derived from references 14-18

[c] Patients compared with literature reference data by the unpaired two-tailed t-test

[d] No data available

hypopituitarism were lower, indicating a more reduced QoL; according to the NHP, no obvious difference in scores was observed.

Linear regression

Stepwise, uni-variate, linear regression analysis was performed in a model including gender, age, radiotherapy, multiple pituitary deficiencies/panhypopituitarism, multiple operations and visual defects as independent variables, and the questionnaire items as dependent variables. Visual field defect was an independent predictor for depression (HADS, $P = 0.05$), total HADS score ($P < 0.05$), reduced activity (MFI-20, $P = 0.05$), reduced motivation (MFI-20, $P < 0.01$) and reduced energy (NHP, $P < 0.05$). Female gender was an independent predictor for depression (HADS, $P < 0.05$), reduced motivation

(MFI-20, P < 0.05) and pain (NHP, P =0.05). Radiotherapy was an independent predictor for mental fatigue (MFI-20, P < 0.05). Repeat surgery correlated to role limitations due to emotional problems (SF-36, P < 0.05). Multiple pituitary deficiencies/panhypopituitarism was not an independent predictor for any of the questionnaire items.

DISCUSSION

Despite long-term cure, adult craniopharyngioma patients experience a considerable decrease in QoL. The decrease in QoL was mainly manifested in the physical items and, to a lesser extent, in psychosocial items. QoL in adult craniopharyngioma patients is mostly affected by visual impairments and to a lesser extent by female gender, repeat surgery and radiotherapy.

The survival prognosis of patients treated for craniopharyngioma is favourable, with reported 10-year survival rates of approximately 90% in both adults and children (1;11;25-27), although a lower survival rate has been reported (6). Clinical symptoms may arise from both tumour mass effects and effects of treatment. In addition to the well-recognized signs and symptoms secondary to hormonal deficiencies and visual deficits, patients experience physical and neuropsychological deficits, such as obesity and deficits of higher cortical function, memory, and behaviour (1;11;13). Decreased QoL in children treated for craniopharyngioma has been reported, affecting both physical and psychosocial health (2;3;11-13). To date, structured QoL research in adult patients treated for craniopharyngioma has been studied in only one report (3). In this study, using the NHP and the QoL-AGHDA questionnaires, QoL was markedly reduced. Our series reports a broader assessment of QoL, which also focuses on fatigue and energy (MFI-20), as well as anxiety and depression (HADS). We applied four different questionnaires, covering multiple aspects of physical, psychological, as well as social functioning.

In the present study, QoL in patients treated for craniopharyngioma proved to be more affected in items concerning physical performance than in psychosocial performance. General fatigue, physical fatigue, energy, physical condition and mobility were significantly affected, as compared with controls. This is in agreement with the high prevalence of metabolic and visual morbidity found in adult craniopharyngioma, which is attributed to irreversible hypothalamic, and optic damage (3;4). Accordingly, the main independent predictors to affect QoL were found to be visual field defects, and to a lesser extent multiple operations, female gender and radiotherapy. However, because of the relative small number of patients, the results of the linear regression analysis have to be interpreted with caution. Multiple pituitary deficiencies or panhypopituitarism was found in all except two craniopharyngioma patients. Because of the small number of patients with intact pituitary function, the potential contribution of hypopituitarism to the reduced

QoL could not statistically be assessed. Hypopituitarism was found to be an independent predictor of reduced QoL in patients treated for Cushing's disease and acromegaly, affecting both physical and psychosocial items (7;9). Despite optimal substitution, it is likely that hypopituitarism in our patient group also contributes to a reduced QoL. SF-36 scores from our craniopharyngioma patients, 93% of whom had pituitary deficiencies in at least three axes, were comparable to scores in patients with two or three pituitary deficiencies after treatment for nonfunctioning pituitary adenomas (8). However, compared to scores from treated Cushing patients with hypopituitarism (9), our craniopharyngioma patients report better QoL scores in all four questionnaires, pointing to a significant contribution of hypercortisolism on reduced QoL.

The predisposition for female gender as an independent risk factor for a decreased QoL in craniopharyngioma is unclear, although it does not seem to be a disease specific phenomenon. In the general population female gender is also associated with higher scores on the NHP, indicating a lower QoL (14). QoL studies in non-pituitary diseases (malignancies, coronary heart disease, inflammatory bowel disease) also report decreased QoL in female patients as compared with male patients (28-32).

Thirty-three of 43 (77%) patients returned the questionnaires, four of whom preferred not to participate because of physical invalidation. Participation of these 4 patients, however, would even have worsened QoL scores, because they suffered of serious morbidity. The use of controls chosen by the patients may have introduced a bias, since controls with a supposedly good QoL are more likely to be asked. In order to overcome this possible bias we also used validated reference data from literature (14-18). Compared with those age-adjusted reference values, QoL parameters were affected significantly in fewer subscales, than was revealed by the comparison with our own controls. This suggests that patients have chosen controls with a supposed good health status. Nonetheless, the comparison with both sources of control data revealed the same pattern, i.e. adult craniopharyngioma patients had seriously impaired QoL.

In conclusion, QoL in adult craniopharyngioma patients is significantly reduced compared to a healthy population, especially in the physical items. The main independent predictor of a worse QoL is visual field defects. Despite long-term cure, treatment of craniopharyngioma, with the aim to prevent recurrence, does not normalize Quality of Life.

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General discussion and summary

CHAPTER 8

In this thesis we have evaluated the effects of treatment and long-term follow-up in patients treated for nonfunctioning pituitary macroadenoma (NFMA) at the Leiden University Medical Center. In the general discussion we will address the following issues:

- Natural course and growth of nonfunctioning pituitary macroadenomas
- Treatment of nonfunctioning pituitary macroadenomas
- Follow-up strategy after surgical treatment
- Long-term effects of treatment for nonfunctioning pituitary macroadenomas

I. NATURAL COURSE AND GROWTH OF NONFUNCTIONING PITUITARY MACROADENOMAS

The natural course of pituitary adenomas

The natural course of NFMA is largely unknown, because the majority of patients with NFMA are operated. Therefore, the primary goal of the study described in **chapter 2** was to asses the natural course of NFMA. In that study, consisting of 28 consecutive non-operated patients with NFMA, with a mean follow-up period of more than 7 years, tumor growth was observed in 50% of the patients. Our results show a higher number of patients with tumor growth compared with the increase in tumor size in approximately 25% of all patients presented in four other studies (1-4). The longer duration of follow-up, and the method of tumor measurements, might account for the higher number of patients with tumor growth in our series compared with previous studies.

In pituitary microadenomas in general, tumor growth is observed in only a minority of the patients. Moreover, in microadenomas, the chance of tumor growth seems to be almost outweighed by the chance of a decrease in tumor size (2;4). Accordingly, the low prevalence of macroadenomas in autopsy series also suggest that growth from microadenoma to macroadenoma is a rare event (5). In patients with macroadenomas the tumor already has demonstrated a propensity for growth. Remarkably, a spontaneous decrease in tumor volume was observed in 29% of the patients during long-term follow-up, whereas in 21% of all patients, tumor volume remained stable (**chapter 2**).

Clinical implications. Nonfunctioning pituitary macroadenomas will not invariable increase in tumor volume during follow-up. Even in the case of tumor growth, there is considerable individual variability. Moreover, tumor volume may even decrease during long-term follow-up. Therefore, the mere presence of NFMA, in the absence of visual field defects, is not a solid indication for surgery.

Predictors of tumor growth

It would be a major advantage to predict tumor growth in individual patients presenting with NFMA, because this would allow individualized strategies for treatment and follow-up. Therefore, we evaluated determinants and predictors of tumor growth in our patients. In case of a conservative treatment strategy, only clinical characteristics can be used, whereas in patients after surgical treatment both clinical and histopathological characteristics could be used for predicting tumor growth.

In our series of patients with non-operated NFMA, there were no independent predictors for increase or decrease in tumor volume as assessed by binary logistic regression (**chapter 2**). Regression analysis was performed in a model including increase and decrease in tumor volume as dependent variables and age, gender, tumor volume, tumor extension, hypopituitarism, prolactin levels and follow-up duration as independent variables.

Clinical implications. In non-operated patients with NFMA, no determinants are available that can predict an increase or decrease in tumor volume in individual patients.

Pituitary apoplexy

Pituitary apoplexy is an infrequent, but potential life-threatening (6), complication of pituitary tumors. It is caused by sudden haemorrhage or infarction of the tumor (7). The estimated prevalence of apoplexy in patients with pituitary tumors is less than 1% (4). In unselected patients with NFMA, apoplexy is the presenting sign in ~20% of all patients (8) (**chapter 3**).

The optimal treatment for NFMA patients presenting with pituitary apoplexy is still a matter of debate (9-11). Because adrenal failure can be present (10;11), there should be no delay in steroid-replacement therapy. In patients presenting with total or near-total visual loss, surgical intervention is indicated. After transsphenoidal surgery visual impairment and ocular paresis resolve in the majority of cases (9-11). However, conservative management with careful follow-up is appropriate in selected patients without, or with only mild, neuro-ophtalmic signs, without adversely affecting patient outcomes (9;12). We described four patients with NFMA, who presented with pituitary apoplexy. In 3 of them, apoplexy was accompanied by visual field defects **(Chapter 2).** In all these 3 patients visual fields normalized spontaneously within three months. In 1 of the 4 patients with pituitary apoplexy, initial pituitary deficiencies were present in 3 of 4 axes, including ACTH deficiency. In this patient, pituitary deficiencies resolved spontaneously within three months.

Clinical implications. Conservative management with close and careful follow-up is a safe initial approach in selected NFMA patients with pituitary apoplexy.

II. TREATMENT FOR NONFUNCTIONING PITUITARY MACROADENOMAS

Indications for surgical treatment

In general, nonfunctioning pituitary microadenoma, do not cause complaints. Because microadenomas do not exceed the anatomical boundaries of the sella, they do not cause visual field defects. The chance of tumor growth in microadenomas is almost outweighed by the change of a decrease in tumor size (2;4). This underscores the widely accepted point of view that in nonfunctioning microadenomas a wait-and-see approach is appropriate.

Pituitary macroadenomas frequently induce visual field defects and pituitary insufficiencies (13-15). Transsphenoidal surgery is the cornerstone in the treatment of nonfunctioning macroadenomas. The main targets in the treatment strategy for patients with NFMA are the restoration of visual function and adequate long-term tumor control. Because pituitary macroadenomas will not invariable lead to tumor growth, visual dysfunction caused by the macroadenoma is the main indication for surgical treatment.

The optimal treatment strategy in patients with a nonfunctioning macroadenoma and normal visual fields is unclear (3;16;17). However, a more detailed analysis of the natural course of nonfunctioning pituitary macroadenomas may select patients in whom a conservative approach is appropriate. In our series of 28 patients in whom an expectant approach was undertaken, in 6 of the 14 patients with tumor enlargement, tumor growth was accompanied by visual field defects. Because the presence of visual field defects is an indication for transsphenoidal surgery, these patients were operated. This means that, of the total of 28 patients, after 7 years of follow-up, in only 21% surgical intervention was indicated (**chapter 2**). Moreover, in all patients operated for tumor growth and visual field defects, these defects improved or normalized. These data suggest that in case of the development of visual field defects during conservative follow-up of NFMA, surgical outcome still is favourable with respect to visual field defects.

Clinical implications. The major indication for surgical treatment in patients with NFMA is the presence of visual field defects. In the absence of visual impairments, observation alone is a safe alternative for surgery in selected patients with NFMA, since surgery can be withheld in more than 75% of cases, without adversely affecting patient outcome.

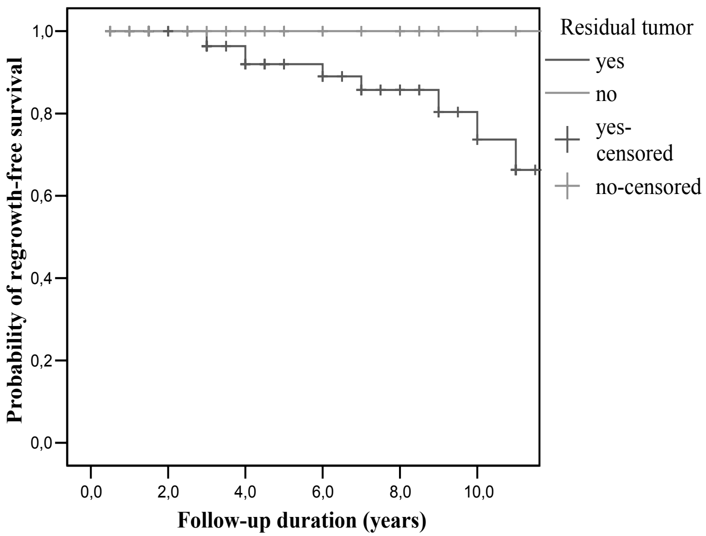
Effect of transsphenoidal surgery on recurrence during long-term follow-up

The natural course of NFMA after transsphenoidal surgery has not been fully elucidated. Therefore, we have evaluated the effect of transsphenoidal surgery on long-term tumor control in patients with nonfunctioning macroadenomas (**chapter 3**). The patients series consisted of 97 consecutive patients treated for nonfunctioning macroadenoma, of whom only 6 were treated with postoperative radiotherapy. The duration of follow-up after surgical treatment was 6.0 years. In only 10% of all patients tumor growth was observed, after a mean follow-up of 6.3 years (range 3-11 years). In patients with residual tumor on MRI, recurrence free survival rates 5 and 10 years after initial surgical treatment were 92% and 74% respectively (Figure 1). In patients without residual tumor, recurrence free survival rates 5 and 10 years after initial surgical treatment, were 100% and 100% respectively.

Our series indicate that, after 10 years of follow-up, only 20% of the patients operated for nonfunctioning macroadenomas will develop tumor recurrence. However, even in the case of tumor recurrence after transsphenoidal surgery, there is considerable individual variability (**chapter 3**). This variability is in accordance with the variability in tumor growth in non-operated patients (**chapter 2**). Because the follow-up duration in patient-series after transsphenoidal surgery, including our study, is limitated to only 6 years, prolongation of this follow-up duration may result in a higher rate of recurrence or tumor regrowth than appreciated by the currently available data. In this respect, a study from Breen *et al.* is of specific interest (6). In a series of operated and irradiated patients with NFMA, they demonstrated tumor control in 88%, 78% and 65% respectively after 10, 20 and 30 years of follow-up. This implicates that there might be no decrease in the chance of tumor recurrence, even 30 years after initial treatment.

Clinical implications. Good tumor control is achieved by transsphenoidal surgery without postoperative radiotherapy for nonfunctioning macroadenomas, even during long-term follow-up. In the considerations with respect to postoperative treatment, it should be noted that only a small percentage of patients will develop tumor recurrence during long-term follow-up.

Figure 1. Kaplan Meier curve for growth-free survival rates in patients with and without residual tumor



Determinants and predictors of tumor recurrence after surgical treatment

The determinants of tumor recurrence after surgical treatment for NFMA are largely unknown. We therefore evaluated the predictors and determinants of tumor recurrence after surgery. In our series of patients treated by transsphenoidal surgery, the only determinant of tumor recurrence was duration of follow-up **(chapter 3)**. Gender, prophylactic radiotherapy, positive immunohistochemistry for pituitary hormones, positive immunohistochemistry for ACTH, and parasellar/infrasellar tumor extension were no independent predictors for tumor growth.

It is reasonable to assume that an increase in tumor recurrence is to be expected in patients in whom pituitary adenoma is not completely resected. This is the case in all patients with parasellar or infrasellar tumor expansion (18). In several other studies the presence of postoperative residual tumor on MR imaging was an independent predictor of tumor recurrence (19;20). In our study, the statistical analysis also pointed towards residual tumor as predictor for tumor recurrence, although this did not reach statistical significance ($p=0.1$). It should be realized that the methods to estimate the presence of residual tumor are imperfect in those patients. The opinion of the surgeon regarding the completeness of tumor removal, underestimates residual tumor (19). Moreover, microscopic dural invasion was found in 94% of all macroadenomas with suprasellar extension (21). This underscores the notion that even postoperative MR imaging may underestimate residual tumor.

The clinical relevance of ACTH-positive immunohistochemistry for patients with NFMA is still under debate. Some studies suggested a more aggressive behaviour of ACTH-positive adenomas and advised postoperative radiotherapy in these patients (22-24). However, increased recurrence rates in patients with ACTH-positive immunostaining could not be shown in the majority of the reports (19;22;25), like in our study (**chapter 3**).

Although DNA ploidy is frequently used to distinguish benign from malignant neoplasms, this is not a predictor for tumor growth in NFMA (26). Moreover, no correlation was found between histological proliferation and apoptosis markers and tumor recurrence (27), nor between nuclear atypia and tumor behaviour (26). A correlation has been described between Ki-67, a marker for cell proliferation, and tumor invasiveness, although this is not established in all reports (24). Therefore, the search for histopathological predictors of tumor behaviour has thus far been disappointing.

Clinical implications. There are no good determinants to predict tumor recurrence in patients after surgical treatment for NFMA, with the exception of follow-up duration, and, probably, indicators of postoperative residual tumor. Nonetheless, in our opinion there are no solid parameters to guide prophylactic postoperative radiotherapy.

Effect of surgical treatment on visual and endocrine outcome

Improvement of visual dysfunction is the main goal of surgical treatment in pituitary macroadenomas by decompression of the optic chiasm. In **chapter 3** we showed improvement in visual function in ~ 80% of all patients after transsphenoidal surgery, comparable with rates reported in other retrospective studies (13;19). The initial event in the pathogenesis of decreased visual function in pituitary macroadenomas is compression of the optic chiasm. This nerve compression leads to decreased conduction and to demyelination (28;29). The improvement of visual dysfunction after surgical treatment, consists of two and, probably even three, phases (30). There is an early phase, comprising the first hours and days after surgery. In this early, fast phase, the improvement is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual recovery has been demonstrated in the first days after surgical treatment (30;31). The phase of delayed recovery is pathophysiologically explained by remyelination of the optic nerves. This phase of delayed recovery may even last several years (30;32). It is already known that visual acuity improves in the first months after surgical treatment (33-37) and that the improvement of visual field defects is a continuing process for at least one year (30;32). The contribution of the first phase of recovery might be larger, given the fact that more than 50% of the final recovery occurs within the first 3 months after surgery (32).

In **chapter 4** we have demonstrated that improvement of visual acuity continued also until one year after surgical treatment for NFMA. After initial, early post-surgical recovery, in the delayed phase a progressive improvement of visual acuity is likely to occur at least until one year after transsphenoidal operation.

Surgical treatment did not reverse pituitary deficiencies in our study (**chapter 3**). Data from other studies concerning postoperative pituitary function are conflicting. Some studies report, to a variable degree, an improvement in pituitary function (38-42), whereas others could not demonstrate significant improvement in pituitary function (13;15;18) or even reported a decrease in pituitary function (43;44).

Clinical implications. Improvement of visual field defects and visual acuity is achieved in the majority of patients after surgery for NFMA. The improvement of visual acuity continues until one year after surgical treatment. In contrast to visual function, pituitary function is not likely to be restored after transsphenoidal surgery. Therefore, the aim of surgery should be improvement of visual function, rather than improvement of pituitary function.

The role of postoperative radiotherapy

The role of the application of postoperative radiotherapy in patients operated for non-functioning pituitary macroadenomas is still under debate. Several retrospective studies have evaluated the effects of long-term follow-up in *unselected, consecutive* patients after surgery for NFMA (13;14;18-20;25;45). All these studies have a follow-up period of ~ 5 years. Recurrence rates in patients without postoperative radiotherapy is reported in 11 to 46% of all patients, whereas recurrence rates after postoperative, prophylactic radiotherapy ranged between 2-36% during long term follow up. These data suggest that postoperative radiotherapy results in a slightly decreased number of recurrences during long-term follow-up (20;25). In our series, in 6 patients treated with prophylactic radiotherapy no tumor recurrence was observed (**chapter 3)**.

The small benefit of postoperative radiotherapy, *i.e.* a decrease in long-term recurrence rate of NFMA, has to be balanced against potential side effects of radiotherapy. Radiotherapy induces increased pituitary deficiencies, a side-effect which is independent of tumor recurrence (46-48). Increased mortality is reported in patients with hypopituitarism, compared with age-matched controls (49-52). In addition to very rare complications of radiotherapy such as optic nerve atrophy and visual deterioration (48;53;54), there is about 2.5% cumulative risk of second brain tumors 20 year after radiotherapy (6;55). Finally, there are indications that radiotherapy for pituitary adenomas may adversely affect quality of life (56).

In our series without postoperative radiotherapy, long-term tumor control was achieved in the absence of recurrence/recurrence in 89% of all patients (**chapter 3**). Even in the case of residual tumor, in 87% of the patients no tumor recurrence was observed. These data, observed after six years of follow-up, show that a treatment strategy without postoperative radiotherapy is effective and do not justify the routine application of prophylactic postoperative radiotherapy in patients with residual tumor after surgery. Moreover, in the case of recurrence during long-term follow-up, radiotherapy is still effective to stabilize or regress tumor growth (25). With this restrictive treatment strategy, the majority of patients will not be exposed to potential long-term sequelae of radiotherapy, whereas in patients with recurrences the starting point of radiotherapy is delayed for several years. This is an important consideration given the fact that potential side-effects of radiotherapy may take years to develop. Nonetheless, postoperative radiotherapy might be considered in selected patients with incomplete tumor removal, large residual tumor and panhypopituitarism. Because data concerning the role of ACTH-positive immunostaining as predictor for tumor growth are conflicting (19;22;25;57), in our opinion, positive immunostaining for ACTH is no indication for postoperative radiotherapy.

Clinical implications. Adequate tumor control can be achieved by transsphenoidal surgery for NFMA in the absence of postoperative radiotherapy. This indicates that a treatment strategy without postoperative radiotherapy is both effective and safe, and will prevent that a large number of patients are exposed to potential long-term sequelae of radiotherapy without having any benefit.

New treatment modalities

Radiosurgery. The main difference between radiosurgery and conventional radiotherapy is given by the fact that radiosurgery is given in one large, much focussed, dose, and conventional radiotherapy in multiple doses. In theory, the major advantage of radiosurgery is decreased locoregional irradiation outside the tumor, with increased sparing of normal pituitary tissue. This is achieved by the combination of better immobilization and high definition 3 dimensional imaging (58). The application of radiosurgery in NFMA patients with residual or recurrent disease after surgical treatment, leads to tumor control in more than 90% of all patients (59-62). Due to the fact that most patient series have a relatively short follow-up period, the long-term effects of radiosurgery on pituitary function and visual function have not been established. Moreover, long-term results comparing radiosurgery with conventional radiotherapy, both for residual as well as recurrent disease, are lacking.

Medical treatment. Treatment of patients with nonfunctioning macroadenomas with dopamine agonists has gained renewed interest, although previous studies using dopamine agonists in these patients have given disappointing results (63-65). Two aspects of dopamine therapy account for this renewed interest:

1. The development of cabergoline, which has a longer duration of action, and a higher specificity and affinity for the D2-receptor (66)
2. The association of D2-receptor expression with the effect of dopamine agonists in nonfunctioning adenomas, both in vitro and in vivo (67).

Recently, Greenman *et al.* studied the effect of dopamine agonists on nonfunctioning adenomas (68). In that study successful treatment was defined as the absence of tumor growth, whereas most previous studies used the reduction of tumor volume as marker for therapeutic effect (63;64). However, in the absence of visual disturbances, the main therapeutic goal is prevention of tumor growth, not necessarily a decrease in tumor volume. Good tumor control in patients with residual adenoma after initial surgical treatment was reported in 90% of patients treated with dopamine agonists, compared with 39% of patients without dopamine therapy (68).

D2-receptor expression was found in 67% of patients operated for NFMA (67). Moreover, the presence of D2-receptor expression was predictive for the effectiveness of dopamine agonists (67). These findings implicate that, in selected patients, treatment of NFMA with dopamine agonists is possible. However, the role of dopamine agonists has to be established in more detail (69). For now, it is unclear whether this treatment is effective as initial treatment, after surgery in order to prevent recurrence, or after recurrence as an alternative for radiotherapy.

Clinical implications. Radiosurgery has some theoretical advantages and good tumor control during short-term follow-up has been reported. D2-receptor expression is a potentially interesting target for cabergoline treatment in NFMA patients. However, the role of both radiosurgery and dopamine agonists in the treatment of NFMA, is not established in detail.

III. FOLLOW-UP STRATEGY AFTER SURGICAL TREATMENT

Ophthalmologic follow-up

The initial aim of postoperative visual assessment is evaluation of the effects of surgical treatment. Improvement of visual function has been shown until one year after surgical treatment (30;32) (**chapter 4**). Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmologic assessment within several weeks after surgery, but also subsequent assessments after one and two years, in order to estimate the final effect of surgical treatment on visual function. These data serve as baseline values for potential tumor recurrence in the long-term.

The role of visual assessment for detection of tumor growth is limited. Although visual assessment is a sensitive tool, its use is limitated due to the low negative predictive value. In our series tumor growth was accompanied by visual field defects in only half of the patients (**chapter 2 and 3)**, comparable with results of other reports (1;2;4).

Clinical implications. Patients should be informed about the likelihood of prolonged improvement of visual function after surgery. Especially in those patients with severe compromised visual function, an increase in visual acuity can have dramatic impact on social functioning. Because tumor growth is not invariable accompanied by visual field defects, assessment of visual function is not a sensitive tool for the detection of tumor growth or recurrence.

Radiological follow-up

The mean reason for post-operative MR imaging is evaluation of the effectiveness of surgery. However, after resection of a pituitary tumor, due to packing materials, postoperative debris, thickened mucosa and blood, there may be no reduction of tumor seen on MR imaging (70). In time, these postoperative features may resolve and the packing material may resorb, leading to reduction in tumor volume over months (70). Therefore, it is reasonable to assess the effectiveness of surgery 4-6 months after initial surgery.

In NFMA patients in whom a conservative postoperative approach is chosen, as well as in patients after transsphenoidal surgery, the rate of tumor growth can not be predicted in individual patients. It is a reasonable approach to repeat MR imaging one year after initial diagnosis, in order to make a first estimation of eventual tumor growth. However, in **chapter 2**, the mean increase in diameter was only 0.6 mm/year in patients with tumor growth, which is below the detection limit of MRI. These data suggest that, for further follow-up, an approach with a repeat MRI every 2-3 year is safe and optimal for detection of possible tumor growth. Moreover, it is important to compare sequential MRI's with the first postoperative MRI, because the increase in tumor volume might be too small to detect on subsequent MRI's.

Clinical implications. Velocity of tumor (re)growth can not be predicted in individual patients after conservative or surgical management for NFMA. In order to discover patients with rapid tumor grow, a repeat MRI should be performed one year after initial diagnosis in patients with a conservative approach, and at 6 months after initial surgical treatment in operated patients. During long-term follow-up, a repeat MRI every 2-3 year is a safe approach.

IV. LONG-TERM EFFECTS OF TREATMENT FOR NONFUNCTIONING PITUITARY MACROADENOMAS

Quality of life

In 1948, the World health organization defined health not only as the absence of disease, but also as the presence of physical, mental and social well-being (71). Quality of Life (QoL) assessment is the method to investigate the physical, psychological and social well-being of the patient. Disease and treatment are being evaluated in terms of the effect on physical, psychological and social functioning. The outcomes of these assessments are, by definition, influenced by patient's beliefs, expectations and perceptions (71). This is an important consideration because for any given disease the medical point-of-view and the patient-point-of-view may not be congruent, especially in chronic diseases (72). QoL assessment will enable physicians to provide adequate information about the impact of pituitary diseases on patient's health.

We evaluated QoL in patients treated for NFMA and craniopharyngioma by four validated health-related questionnaires (HADS, MFI-20, NHP, SF-36), comparing patients outcomes to controls groups **(chapters 6 and 7).** In patients treated for NFMA or craniopharyngioma, QoL is decreased compared with control subjects as well as to age-adjusted reference values**.** Compared with our own control values, patients treated for NFMA reported a decreased QoL in 18 out of 21 subscales, craniopharyngioma patients in 11 out of 21 subscales. This most likely underscores the supposed good health status in patient derived controls (73). However, also compared with reference values derived from literature, patients treated for NFMA reported a significantly decreased QoL in 10 out of 21 subscales and patients treated for craniopharyngioma in 5 out of 21 subscales.

In both NFMA and craniopharyngioma patients almost all items concerning energy and fatigue were affected. Moreover, both patient groups reported reduced physical activity and physical mobility and physical functioning. Linear regression analysis revealed the presence of multiple pituitary deficiencies (NFMA) and visual impairments (craniopharyngioma) as the predominant predictors of a decreased QoL. Quality of life was, to a lesser extend, also affected by age, female gender, repeat surgery and radiotherapy. In patients treated for NFMA, the presence of multiple pituitary deficiencies was the most predominant predictor for decreased QoL (**chapter 6**), pointing towards an important role of pituitary function for optimal QoL (56). The effects of hormones in general are difficult to quantify at the tissue level. Moreover, hormonal substitution therapy does not reproduce the normal plasma hormone profiles of healthy individuals (74). These intrinsic imperfections in endocrine replacement therapy may result in subtle physiological derangements. Most importantly, this imperfection in endocrine substitution may result in a decreased QoL. However, we could not properly assess the effect of hypopituitarism per se on QoL, because hypopituitarism was present in 93% of all NFMA patients and in all craniopharyngioma patients.

The 4 health-related questionnaires used in this study, were not disease-specific, i.e. they were not developed to assess QoL in NFMA or craniopharyngioma patients, although the NHP is frequently used in patients with pituitary disease. However, we found a reduced QoL in the majority of subscales of the MFI-20, the SF-36 and the NHP. This seems to point towards a strong overall effect of the pituitary diseases on general health and well being, of both the physical and the psychosocial aspects.

A limitation of the assessment of QoL is that QoL can not be directly measured. It has to be measured indirectly by several questions which are supposed to cover a 'true' QoL (71). Because QoL is not directly measured but inferred from quantitative scoring systems, it might be possible that the perception of the patient of their QoL is not congruent with the quantitative outcomes as measured by QoL questionnaires.

Clinical implications. Despite long-term cure in patients treated for both nonfunctioning pituitary adenoma and craniopharyngioma, QoL is significantly reduced compared with a healthy population, especially in the physical items and items concerning energy (**chapter 6 and 7**). These irreversible effects of these pituitary diseases have to be taken into account by doctors in the assessment of these patients.

Mortality in patients with pituitary adenomas

A number of studies have reported increased mortality in patients with pituitary tumors (49;75-79) and associated conditions such as hypopituitarism (50-52). In the majority of studies the general population was used as control group to assess mortality in pituitary adenomas. However, it is presently unknown to what extent the excess mortality is caused by pituitary tumors and their treatment in general, and to what extent by (previous) exposure to cortisol or growth hormone (GH) overproduction.

In **chapter 5** we evaluated mortality rates during long-term follow up of patients with pituitary adenomas treated by transsphenoidal surgery. Because mortality in pituitary adenomas is associated with both general aspects of pituitary tumors and disease specific morbidity, we compared mortality in patients with Cushing's disease and acromegaly to mortality in patients treated for NFMA. Patients treated for NFMA lack the morbidity conditions specific for acromegaly or Cushing's disease.

The increased mortality in operated patients with pituitary adenomas is associated with several factors, some of which are associated with pituitary tumors in general and some of which are disease specific. Transsphenoidal surgery is associated with a perioperative mortality of ~ 0.9% (80;81). Hypopituitarism, present in the majority of patients treated for pituitary macroadenomas, is associated with increased mortality (51;52). Several studies reported increased cardiovascular and cerebrovascular mortality in patients with pituitary diseases other than acromegaly and Cushing's disease (50;52;77-79). Although the exact mechanisms by which hypopituitarism is causing increased mortality are unclear, there are suggestions that hypopituitarism is associated with vascular disease (50;82-84). Several authors point towards the role of untreated GH-deficiency in this respect (50;85). Cortisol excess induces central obesity, diabetes mellitus and hypertension (86). These effects are reversed upon cure of Cushing's disease. However, it has been suggested that cortisol overproduction is associated with increased cardiovascular risk, continuing even after remission of the disease (87;88). Therefore, the effects of transient cortisol overproduction may not be reversible with respect to certain biological properties that influence mortality.

The mortality rate for the whole cohort in our study was increased by 41%, compared with the general population, despite adequate treatment **(chapter 5)**. In addition, the mortality risks appeared to be different among the three pituitary diseases. The standardized mortality ratio (SMR) in NFMA patients was 1.24 (95% CI 0.82-1.74). In patients with Cushing's disease the SMR was 2.39 (95% CI 1.22-3.9). Moreover, after transsphenoidal surgery for Cushing's disease there is an increased mortality risk compared with both NFMA and acromegaly. This points towards cortisol effects on increased mortality in patients with Cushing's disease, because treatment and medical care were comparable between patients with Cushing's disease and both patients with NFMA or acromegaly. Moreover, it implies that previous, transient overexposure to cortisol is associated with increased mortality, despite long term normalisation of cortisol levels in the majority of patients. The importance of cortisol in mortality excess is established by the fact that mortality is increased in patients with persistent disease, compared with cured patients (89;90).

Clinical implications. The relative mortality risk is increased in patients with Cushing's disease compared with both NFMA and acromegaly. This implicates that exposure to cortisol excess is a major contributor of the increased mortality even after cure of Cushing's disease.

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Discussie en samenvatting

CHAPTER 9

In dit proefschrift hebben we de effecten geëvalueerd van zowel behandeling, als van lange termijn follow-up bij patiënten, behandeld voor een niet-functionerend hypofyse macroadenoom (NFMA). Alle patiënten werden behandeld en vervolgd in het Leidsch Universitair Medisch Centrum. In deze algemene discussie zullen de volgende aspecten aan de orde komen:

- Natuurlijk beloop en groei van niet-functionerende hypofyse macroadenomen
- Behandeling van niet-functionerende hypofyse macroadenomen
- Follow-up strategieën na chirurgische behandeling
- Lange termijn effecten van behandeling voor niet-functionerende hypofyse macro-adenomen

I. NATUURLIJK BELOOP EN GROEI VAN NIET-FUNCTIONERENDE HYPOFYSE MACROADENOMEN

Het natuurlijke beloop van hypofyseadenomen

Het natuurlijke beloop van NFMA's is voor een belangrijk deel onbekend omdat het merendeel van de patiënten met een NFMA geopereerd wordt. Het primaire doel van de studie, zoals in **hoofdstuk 2** beschreven, was dan ook het natuurlijk beloop van NFMA in kaart te brengen. In deze studie, bestaande uit 28 patiënten, met een gemiddelde follow-up van meer dan 7 jaar, werd bij 50% van de patiënten groei van het NFMA gezien. De incidentie van groei van NFMA is iets hoger dan gerapporteerd in eerdere studies, die een tumorgroei bij ongeveer 25% van alle niet-geopereerde NFMA patiënten laten zien (1-4). De langere follow-up duur, evenals het verschil in methode om het tumorvolume te meten, kunnen ten grondslag liggen aan het hogere percentage patiënten met tumorgroei in onze studie.

Bij patiënten met een hypofyse microadenoom wordt slechts bij een klein deel van de patiënten tumorgroei gezien. De kans op tumorgroei bij deze patiënten is ongeveer even groot als de kans op afname in tumor volume (2;4). Dit gegeven is in overeenstemming met het feit dat in grote autopsie-series het vóórkomen van macroadenomen zeldzaam is (5). Daarentegen heeft bij patiënten met een NFMA de tumor reeds aangetoond te kunnen groeien. Het is opvallend dat in onze studie (hoofdstuk 2) een spontane reductie in tumorvolume werd gezien bij 29% van alle patiënten gedurende follow-up, terwijl in 21% er geen verandering in tumorvolume werd waargenomen.

Klinische implicaties. NFMA's leiden niet in alle gevallen tot een toename in tumor volume gedurende follow-up. Zelfs indien sprake is van tumorgroei, is er een grote individuele variabiliteit. Daarnaast kan een NFMA spontaan in volume afnemen. Dit betekent dat de aanwezigheid van een NFMA, bij normale gezichtsvelden, niet zonder meer een operatie-indicatie is.

Voorspellers van tumorgroei

Het zou een groot voordeel betekenen om in individuele patiënten die zich met een NFMA presenteren, tumorgroei te kunnen voorspellen. Dit zou immers een geïndividualiseerde strategie voor behandeling en follow-up mogelijk maken. In onze studie (**hoofdstuk 2 en 3**) hebben we gezocht naar voorspellers en determinanten voor tumorgroei bij patiënten met een NFMA. In het geval van een conservatief beleid kunnen alleen klinisch kenmerken worden gebruikt, bij geopereerde patiënten kunnen naast klinische-, ook histopathologische kenmerken worden gebruikt om tumorgroei te voorspellen.

In de niet-geopereerde patiëntenserie **(hoofdstuk 2)**, bleken geen onafhankelijke voorspellers voor toename of afname in tumorvolume aantoonbaar. De regressie analyse werd uitgevoerd in een model met toename en afname van tumorvolume als afhankelijke variabelen, en leeftijd, geslacht, tumorvolume, tumorextensie, hypopituitarisme, prolactine-spiegels en duur van follow-up als onafhankelijke variabelen.

Klinische implicaties. In niet-geopereerde patiënten met een NFMA blijken geen goede parameters voorhanden die afname of toename van tumor volume in individuele patiënten kunnen voorspellen.

Apoplexie

Hypofysaire apoplexie is een zeldzame, maar potentieel levensbedreigende (6), complicatie van hypofysetumoren. Het wordt veroorzaakt door infarcering dan wel bloeding van de tumor (7). De geschatte prevalentie van apoplexie bij patiënten met hypofyse tumoren is minder dan 1% (4). In een groep met ongeselecteerde NFMA patiënten, is apoplexie het presenterende symptoom bij ongeveer 20% van alle patiënten (8) (**hoofdstuk 3**).

De optimale behandelstrategie bij NFMA patiënten met apoplexie is onderwerp van discussie (9-11). Omdat bijnierinsufficiëntie kan bestaan, moet direct met toedienen van corticosteroïden worden gestart (10;11). Bij patiënten met ernstige visuele disfunctie is een spoedoperatie geïndiceerd. Na transsfenoidale operatie verbeteren gezichtsvelddefecten en visusstoornissen in het merendeel van de patiënten (9-11). Een conservatieve benadering met zorgvuldige follow-up bij geselecteerde patiënten met apoplexie zonder, of met slechts milde oogafwijkingen, is een goede behandeloptie, zonder nadelige effecten (9;12). We beschreven 4 NFMA patiënten die zich met apoplexie presenteerden **(hoofdstuk 2)**. Bij 3 van deze patiënten ging de apoplexie gepaard met gezichtsvelddefecten. In al deze 3 patiënten verbeterden de gezichtsvelden spontaan binnen 3 maanden. Bij 1 van de 4 patiënten was er hypofyse uitval van 3 assen, inclusief de hypofyse-bijnieras. In deze patiënt verbeterde de hypofysefunctie spontaan binnen enkele maanden.

Klinische implicaties. Een afwachtend beleid met zorgvuldige observatie en follow-up is een veilige initiële behandelstrategie bij geselecteerde NFMA patiënten die zich met apoplexie presenteren.

II. BEHANDELING VAN NIET-FUNCTIONERENDE HYPOFYSEADENOMEN

Indicaties voor chirurgische behandeling

Niet-functionerende hypofyse microadenomen veroorzaken in het algemeen geen klachten of symptomen. Omdat microadenomen de anatomische grenzen van de sella turcica niet overschrijden, veroorzaken ze geen gezichtsvelddefecten. Daarnaast is de kans op groei van de tumor bijna even groot als de kans op afname van het tumor volume (2;4). Dit aspect onderstreept de visie dat bij patiënten met niet-functionerende microadenomen een 'wait-and-see' beleid aangewezen is.

Hypofyse macroadenomen induceren vaak gezichtsvelddefecten en hypofyse insufficiëntie (13-15). Transsfenoidale operatie is de hoeksteen in de behandeling van NFMA. Het belangrijkste doel van de behandelstrategie bij patiënten met NFMA is het herstel van visuele functie and adequate lange-termijn tumorcontrole. Omdat hypofyse macroadenomen niet in alle gevallen verder groeien, is visuele disfunctie de voornaamste indicatie voor chirurgische therapie.

De optimale behandeling van patiënten met een NFMA zonder gezichtsvelddefecten is niet geheel uitgekristalliseerd (3;16;17). Echter, meer precieze kennis van het natuurlijk beloop van NFMA's zou tot een selectie van patiënten kunnen leiden waarbij een expectatief beleid geïndiceerd is. In onze serie van 28 patiënten, was bij 14 sprake van tumorgroei tijdens follow-up **(hoofdstuk 2)**. Slechts bij 6 patiënten ging de tumorgroei gepaard met gezichtsvelddefecten. Deze 6 patiënten werden geopereerd omdat gezichtsvelddefecten een harde operatie-indicatie vormen. Dit betekent dat, na ruim 7 jaar follow-up, bij slechts 21% van de initiële patiëntengroep chirurgie geïndiceerd was. In alle 6 gevallen verbeterden de visuele defecten na operatie. Onze studie laat zien dat in het geval zich gezichtsvelddefecten ontwikkelen tijdens een conservatieve behandelstrategie, het effect van chirurgie nog steeds heel goed is.

Klinische implicaties. De voornaamste indicatie voor chirurgie bij patiënten met een NFMA is gezichtsvelddefecten. In de afwezigheid van visusproblemen is een expectatief beleid bij geselecteerde NFMA patiënten een veilig alternatief, omdat in ruim 75% van de patiënten geen chirurgisch ingrijpen noodzakelijk blijkt.

Effect van transsfenoidale chirurgie op tumorrecidief tijdens langdurige follow-up

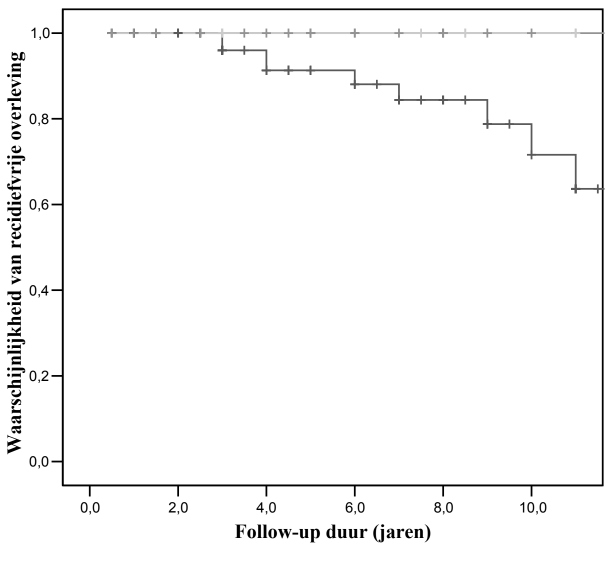
In **hoofdstuk 3** hebben we het beloop van NFMA na transsfenoïdale operatie beschreven. In dit onderzoek werden 97 opeenvolgende patiënten ruim 6 jaar na transsfenoidale operatie gevolgd. Bij 6 van deze patiënten werd postoperatieve radiotherapie gegeven. Bij slechts 10% van de patiënten trad een tumorrecidief op, gemiddeld 6,3 jaar na de initiële operatie (range 3-11 jaar). Bij patiënten met residuaal tumorweefsel op de postoperatieve MRI was de 5 en 10-jaars recidief vrije overleving respectievelijk 92% en

75% (zie figuur 1). Bij patiënten zonder residuaal tumorweefsel waren deze percentages respectievelijk 100% en 100%.

Onze studie laat zien dat 10 jaar na de chirurgische behandeling, slechts bij 20% van alle NFMA patiënten een tumorrecidief is opgetreden. Echter, in het geval van tumor-recidief, is er sprake van een grote individuele variabiliteit (**hoofdstuk 3**). Dit is in overeenstemming met de grote variabiliteit in niet-geopereerde patiënten (**hoofdstuk 2**). Omdat de follow-up in de meeste onderzoeken naar NFMA patiënten na transsfenoidale operatie beperkt is tot ongeveer 6 jaar, is het mogelijk dat verlenging van de follow-up duur hogere recidief percentages zal laten zien. In dit opzicht is een studie van Breen *et al.* interessant (6). In een studie met geopereerde en bestraalde NFMA patiënten laten zij een 10, 20 en 30 jaars recidief vrije overleving van respectievelijk 88%, 78% and 65% zien. Dit impliceert dat er geen afname in de kans op tumorrecidief lijkt te zijn, zelfs niet 30 jaar na initiële behandeling.

Klinische implicaties. Transsfenoidale chirurgie zonder postoperatieve radiotherapie geeft goede tumor controle bij patiënten met een NFMA, ook tijdens lange follow-up. Indien bij individuele patiënten met een NFMA toch postoperatieve radiotherapie wordt overwogen, moet in het achterhoofd worden gehouden dat slechts een klein percentage van de patiënten een recidief zal ontwikkelen.

Figuur 1. Kaplan Meier curve voor recidiefvrije overleving bij patiënten met en patiënten zonder residu tumor na transsfenoidale operatie



Determinanten en voorspellers voor tumorrecidief na operatieve behandeling

De determinanten voor tumorrecidief bij NFMA patiënten zijn voor een belangrijk deel onbekend. Om die reden hebben we gekeken naar voorspellers en determinanten van tumor recidief na chirurgie. In onze studie bij geopereerde NFMA patiënten was de enige determinant voor tumorrecidief de follow-up duur **(hoofdstuk 3)**. Geslacht, profylactische radiotherapie, positieve immunohistochemie voor hypofysaire hormonen, positieve immunohistochemie voor ACTH, and parasellaire/infrasellaire tumor extensie waren geen onafhankelijke predictoren voor tumorgroei.

Het is redelijk om te veronderstellen dat tumor recidieven vaker voorkomen bij patiënten met een incomplete tumorresectie. Dit is per definitie het geval bij alle patiënten met parasellaire of infrasellaire tumorexpansie (18). In verschillende onderzoeken is een verband aangetoond tussen de aanwezigheid van residuaal tumorweefsel op de MRI en de kans op een tumorrecidief (19;20). In onze studie wees statistische analyse eveneens in de richting van tumorresidu als onafhankelijke voorspeller voor recidief, hoewel deze associatie niet significant was ($p=0.1$).

De methoden om een inschatting van de aanwezigheid van residuaal tumorweefsel te maken zijn imperfect. De beoordeling van de chirurg met betrekking residuaal weefsel geeft een onderschatting van het aantal patiënten met tumor residu (19). Daarnaast blijkt bij microscopische onderzoek durale invasie aanwezig te zijn bij 94% van alle patiënten met een macroadenoom met suprasellaire extensie (21). Dit onderstreept het feit dat ook de postoperatieve MRI de aanwezigheid van tumor residu kan onderschatten.

De klinische betekenis van positieve immunohistochemie voor ACTH is onderwerp van discussie. Sommige auteurs suggereren een agressiever beloop bij patiënten met een ACTH-positieve NFMA en adviseren daarom postoperatieve radiotherapie bij deze patiënten (22-24). Daarentegen is een toename van tumorrecidieven bij patiënten met een ACTH-positieve immunohistochemie niet aangetoond in een aantal studies (19;22;25), evenmin als in onze studie (**hoofdstuk 3**).

Hoewel DNA-ploiditeit vaak wordt gebruikt om een onderscheid te maken tussen benigne en maligne tumoren, blijkt dit geen goede predictor voor tumorgroei bij NFMA te zijn (26). Daarnaast werd geen goede correlatie gevonden tussen histologische proliferatie-markers voor apoptose en tumor recidieven (27) evenmin als tussen kern-atypie en tumor groei (26). Er is een correlatie beschreven tussen Ki-67, een marker voor celproliferatie, en tumor invasie, hoewel dit niet in alle studies bevestigd wordt (24). De zoektocht naar histopathologische predictoren voor tumorgroei is, tot dusver, teleurstellend.

Klinische implicaties. Er blijken geen goede determinanten te zijn die tumorrecidief kunnen voorspellen na chirurgische behandeling voor een NFMA, met de uitzondering van follow-up duur en mogelijk determinanten van postoperatief tumorresidu. Dit betekent dat er geen betrouwbare parameters zijn die richtingwijzend zijn voor eventuele postoperatieve radiotherapie.

Effect van chirurgische behandeling op visuele en endocriene functie

Verbetering van visuele disfunctie door opheffen van de chiasma compressie, is het belangrijkste doel van chirurgische behandeling van niet-functionerende hypofyse macroadenomen. In **hoofdstuk 3** hebben we verbetering van visuele functie bij ~ 80% van alle patiënten na transsfenoidale chirurgie laten zien, een percentage dat vergelijkbaar is met andere studies (13;19). Compressie van het chiasma opticum is het eerste event in de pathogenese van verminderde visuele functie door macroadenomen. Deze zenuwcompressie leidt tot een verminderde conductie en demyelinisatie (28;29). De verbetering van de visuele functie na operatie berust op twee, mogelijk drie fases (30). 1) De eerste fase begint de eerste uren en dagen na operatie. Tijdens deze eerste fase wordt de verbetering veroorzaakt door decompressie van het visuele geleidingssysteem, waardoor een herstel van de signaaltransductie optreedt. Herstel van de visuele functie is aangetoond in de eerste dagen na operatie (30;31). 2) De fase van het vertraagd herstel wordt pathofysiologisch verklaard door de remyelinisatie van de zenuwbanen. Deze vertraagde fase kan meerdere jaren in beslag nemen (30;32). Het is bekend dat gezichtsscherpte in de eerste maanden na de operatie verbetert (33-37) en dat verbetering van gezichtsvelddefecten een proces is dat langer dan een jaar kan duren (30;32). De bijdrage aan het herstel van de visus van de eerste fase is waarschijnlijk groter, gegeven het feit dat meer dan 50% van het uiteindelijke herstel optreedt binnen drie maanden na chirurgische behandeling (32).

In **hoofdstuk 4** hebben we aangetoond dat ook verbetering van visus een continu proces is, tot in ieder geval 1 jaar na operatie voor NFMA. Na initiële, postoperatieve verbetering, wordt tijdens de late fase een progressieve verbetering van gezichtsscherpte gezien tot ten minste een jaar na de transsfenoidale ingreep.

Chirurgische behandeling liet geen verbetering van hypofyse functies zien in onze studie (**hoofdstuk 3**). Gegevens van andere studies betreffende het eventuele herstel van hypofysefunctie door operatie, laten tegenstrijdige resultaten zien. Sommige studies vermelden, in wisselende mate, een verbetering van hypofyse functie (38-42), terwijl andere studies geen verbetering (13;15;18) of zelfs een verslechtering van hypofyse functies tonen (43;44).

Klinische implicaties. Verbetering van gezichtsvelden en gezichtsscherpte wordt bereikt in het merendeel van de NFMA patiënten na chirurgische behandeling. De verbetering van gezichtsscherpte is een continu proces dat ten minste een jaar na operatie nog doorgaat. In tegenstelling tot de visuele functie, is het niet waarschijnlijk dat de hypofysefunctie herstelt door transsfenoidale chirurgie van macroadenomen. Het doel van operatie bij NFMA's is dan ook het herstel van visuele functie, niet van hypofysefunctie.

De rol van postoperatieve radiotherapie

Over de rol van postoperatieve radiotherapie bij geopereerde NFMA patiënten bestaat nog steeds discussie. Verschillende retrospectieve studies hebben gekeken naar de lange-termijn effecten in *ongeselecteerde, opeenvolgende* NFMA patiënten na transsfenoidale chirurgie (13;14;18-20;25;45). Al deze studies hebben een follow-up van ~ 5 jaar. Tumor-recidief bij patiënten zonder postoperatieve radiotherapie wordt gerapporteerd in 11 tot 46% van alle patiënten, terwijl het recidiefpercentage bij patiënten met postoperatieve radiotherapie varieert tussen de 2 en 36%. Deze data suggereren dat postoperatieve radiotherapie resulteert in een kleine afname van het recidiefpercentage tijdens lange-termijn follow-up (20;25). In ons onderzoek werd bij de 6 patiënten met postoperatieve radiotherapie geen tumorrecidief gezien (**hoofdstuk 3)**.

Het voordeel van postoperatieve radiotherapie, te weten de mogelijke afname van tumorrecidieven tijdens lange follow-up, moet worden afgewogen tegen de potentiële bijwerkingen van radiotherapie. Radiotherapie induceert een toename van hypofyse insufficiënties (46-48). Een verhoogde mortaliteit is gevonden bij patiënten met hypopituitarisme in vergelijking met leeftijds-gematchte controles (49-52). Naast zeer zeldzame complicaties van radiotherapie als atrofie van de nervus opticus en vermindering van visuele functies (48;53;54), is er een 2.5% cumulatief risico op het krijgen van secundaire hersentumoren 20 jaar na radiotherapie (6;55). Ten slotte zijn er indicaties dat radiotherapie een negatief effect op de kwaliteit van leven heeft (56).

In ons onderzoek, bij patiënten zonder postoperatieve radiotherapie, werd een goede lange-termijn tumor-controle bereikt in 89% van alle patiënten (**hoofdstuk 3**). Zelfs bij patiënten met tumorresidu op de postoperatieve MRI, werd bij 87% van de patiënten geen tumorrecidief gezien. Deze data, met een follow-up duur van 6 jaar, laten zien dat een behandelstrategie zonder postoperatieve radiotherapie effectief is en het toepassen van postoperatieve radiotherapie niet zonder meer rechtvaardigt. Daarnaast blijkt in het geval van een tumorrecidief radiotherapie nog steeds te leiden tot tumorregressie of tumorstabilisatie (25). Met deze restrictieve behandelstrategie, zal het merendeel van de patiënten niet worden blootgesteld aan de potentiële lange-termijn bijwerkingen van radiotherapie, terwijl in het geval van een tumorrecidief het startpunt van de radiotherapie met een aantal jaar wordt uitgesteld. Dit laatste is een belangrijke overweging, gegeven het feit dat potentiële bijwerkingen van radiotherapie pas na vele jaren optreden. Bij geselecteerde patiënten, indien er sprake is van panhypopituitarisme en een groot tumorresidu, kan radiotherapie worden overwogen. Omdat data aangaande de betekenis van ACTH positieve immunohistochemie voor tumorrecidief niet eensluidend zijn, (19;22;25;57), is het onze opinie dat ACTH-positieve immunohistochemie geen indicatie voor profylactische radiotherapie vormt.

Klinische implicaties. Adequate tumorcontrole wordt verkregen door transsfenoidale chirurgie voor NFMA, zonder postoperatieve radiotherapie. Dit betekent dat een behandelstrategie zonder postoperatieve radiotherapie veilig en effectief is, en voorkomt dat een groot aantal patiënten wordt blootgesteld aan de negatieve lange-termijn effecten van radiotherapie, zonder dat hier een duidelijk voordeel tegenover staat.

Nieuwe behandelingen

Radiochirurgie. Het voornaamste verschil tussen radiochirurgie en conventionele radiotherapie is dat radiochirurgie wordt gegeven in een grote, gefocuste dosis, terwijl conventionele radiotherapie wordt toegediend in multipele dosis. In theorie is het grote voordeel van radiochirurgie de verminderde locoregionale stralingsbelasting in weefselgebieden buiten de tumor, waarbij het normale hypofyseweefsel in belangrijke mate gespaard wordt. Dit wordt bereikt door een combinatie van betere immobilisatie en high definition 3 dimensionale beeldvorming (58). De toepassing van radiochirurgie bij patiënten met een NFMA en residuaal tumorweefsel of recidief tumor, leidt bij 90% van de patiënten tot adequate tumor controle (59-62). Omdat in deze onderzoeken de follow-up duur relatief kort is, zijn de lange termijn effecten van radiochirurgie op hypofyse- en visuele functie nog niet duidelijk. Daarnaast zijn, zowel bij patiënten met tumor residu als bij patiënten met tumorrecidief, geen lange-termijn resultaten bekend die radiochirurgie met conventionele radiotherapie vergelijken.

Medicamenteuze behandeling. Behandeling van NFMA patiënten met dopamine-agonisten staat recent weer in de belangstelling, ondanks het feit dat resultaten van dopamine-agonisten in eerdere studies teleurstellend waren (63-65). Twee aspecten van de dopamine-agonisten therapie dragen bij aan deze hernieuwde belangstelling:

1. De ontwikkeling van cabergoline, een dopamine-agonist met een langere werkingsduur en een hogere specificiteit en affiniteit voor de D2-receptor (66)
2. De associatie van de D2-receptor expressie met het effect van dopamine-agonisten, zowel in vivo als ook in vitro (67).

Recent hebben Greenman *et al.* de effecten of dopamine agonisten bij NFMA's bestudeerd (68). In deze studie werd succesvolle behandeling gedefinieerd als de afwezigheid van tumor groei, daar waar veel eerdere studies de reductie van tumor volume als marker voor therapeutisch effect gebruikten (63;64). In de afwezigheid van visusproblemen is echter het primaire therapeutische doel de preventie van tumorgroei, niet noodzakelijk de afname van tumorvolume. Goede tumorcontrole bij patiënten met een recidief adenoom na initiële chirurgische therapie wordt gerapporteerd bij 90% van de met dopamine agonisten behandelde patiënten, vergeleken met 39% van de patiënten die niet met dopamine agonisten werden behandeld (68).

D2-receptor expressie werd gevonden bij 67% van geopereerde patiënten met een NFMA (67). Tevens bleek de aanwezigheid van D2-receptor expressie voorspellend voor het effect van dopamine agonisten (67). Deze bevindingen impliceren dat, bij geselecteerde patiënten, behandeling van een NFMA met dopamine agonisten mogelijk effectief is. De plaats van dopamine agonisten bij de behandeling van NFMA's moet nog verder uitkristalliseren (69). Zo is het onduidelijk of deze behandeling effectief is als initiële behandeling, na chirurgie om recidieven te voorkomen, of na tumorrecidief als een alternatief voor radiotherapie.

Klinische implicaties. Radiochirurgie heeft enkele theoretische voordelen en goede korte termijn resultaten zijn beschreven. D2-receptor expressie is een potentieel interessant target voor therapie met dopamine agonisten. Echter, de rol van zowel radiochirurgie als ook dopamine agonisten bij de behandeling van NFMA, moet nog nader worden onderzocht en uitgewerkt.

III. FOLLOW-UP STRATEGIE NA CHIRURGISCHE BEHANDELING

Oogheelkundige follow-up

Het initiële doel van postoperatieve beoordeling van de visuele functie is de evaluatie van het effect van chirurgie. Verbetering van visuele functie is aangetoond tot een jaar na operatie (30;32) (**hoofdstuk 4**). Follow-up van patiënten na chirurgie voor hypofysaire macroadenomen moet in ieder geval oogheelkundige beoordeling binnen enkele weken omvatten, maar tevens beoordeling na 1 en 2 jaar, om het uiteindelijke effect van chirurgische behandeling op visus te kunnen beoordelen. Deze data dienen dan tevens als uitgangswaarde voor potentiële tumor recidieven tijdens langere follow-up.

De rol van oogheelkundig onderzoek voor de detectie van tumorrecidieven is beperkt. Hoewel beoordeling van gezichtsvelden een sensitieve methode is, wordt de rol beperkt door de lage negatief voorspellende waarde. In onze onderzoeken ging tumorgroei in slechts de helft van de patiënten gepaard met gezichtsvelddefecten (**hoofdstuk 2 en 3)**, een percentage vergelijkbaar met resultaten uit andere studies. (1;2;4).

Klinische implicaties. Patiënten moeten worden geïnformeerd over de mogelijkheid van een langer durende herstelperiode voor de visus na chirurgie. Dit is van belang omdat een verminderde gezichtsscherpte een grote impact op de kwaliteit van leven heeft. Omdat tumorgroei niet altijd vergezeld gaat met gezichtsvelddefecten, is beoordeling van gezichtsvelden geen sensitieve methode om tumorgroei op het spoor te komen.

Radiologische follow-up

De voornaamste reden voor een postoperatieve MRI is het beoordelen van het effect van de chirurgische interventie. Men dient zich bewust te zijn dat een eerste postoperatieve MRI, ten gevolge van postoperatieve debris, verdikte mucosa en bloed, mogelijk geen reductie in tumor volume laat zien (70). Deze postoperatieve veranderingen verdwijnen meestal binnen drie maanden (70). Daarom is het zinnig de eerste MRI na een operatie pas 4-6 maanden na chirurgie te doen.

Bij NFMA patiënten bij wie is gekozen voor een conservatief beleid, evenals bij patiënten na transsfenoidale chirurgie, kan, in individuele gevallen, de snelheid van tumor groei niet goed worden voorspeld. Het is een rationele benadering om een eerste MRI te herhalen na 1 jaar, ten einde een inschatting te maken van de eventuele snelheid van tumorgroei. We hebben echter in **hoofdstuk 2** laten zien dat de gemiddelde toename in diameter bij patiënten met tumorgroei slechts 0.6 mm/jaar was, hetgeen onder de detectiegrens van de MRI ligt. Deze data suggereren dat voor verdere follow-up, een beleid waarbij de MRI elke 2-3 jaar wordt herhaald veilig en optimaal is voor de detectie van tumorgroei. Daarnaast is het belangrijk om bij opeenvolgende MRI's steeds de eerste (postoperatieve) MRI bij de beoordeling te betrekken, omdat de toename in tumorvolume te klein kan zijn om op opeenvolgende MRI's goed in te schatten.

Klinische implicaties. De snelheid van tumorgroei kan, bij individuele patiënten niet goed worden voorspeld, zowel na chirurgie als bij een conservatief beleid van NFMA's. Om patiënten met een snelle tumorgroei op te sporen moet een MRI worden herhaald 1 jaar na diagnose bij patiënten met een conservatief beleid, en 6 maanden na operatie bij geopereerde patiënten. Gedurende de follow-up is het raadzaam de MRI elke 2-3 jaar te herhalen.

IV. LANGE-TERMIJN EFFECTEN VAN BEHANDELING VOOR NIET-FUNCTIONERENDE HYPOFYSE MACROADENOMEN

Kwaliteit van leven

In 1948 werd door de World Health Organization gezondheid niet alleen gedefinieerd als de afwezigheid van ziekte, maar tevens als de aanwezigheid van fysiek, geestelijk en sociaal welbevinden (71). Kwaliteit van leven (KvL) assessment is een methode om fysiek, geestelijk en sociaal welbevinden van de patiënt te onderzoeken. Ziekte en behandeling worden geëvalueerd in termen van om fysiek, geestelijk en sociaal welbevinden. De uitkomsten van dergelijke onderzoekingen worden per definitie beïnvloed door de overtuigingen, verwachtingen en percepties van de patiënt (71). Dit is een belangrijke overweging omdat, voor een willekeurige ziekte, het medische gezichtspunt kan verschillen van het gezichtspunt van de patiënt (72). KvL onderzoek maakt het voor artsen mogelijk om adequate informatie te verkrijgen over de impact van hypofyse ziekten.

We hebben KvL geëvalueerd bij patiënten die zijn behandeld voor NFMA en craniofaryngiomen middels 4-gevalideerde en ziekte gerelateerde vragenlijsten (HADS, MFI-20, NHP, SF-36), waarbij we de patiënten vergeleken met gezonde controles **(hoofdstuk 6 en 7).** Bij patiënten die werden behandeld voor NFMA of een craniofaryngioom, is de KvL duidelijk afgenomen in vergelijking met controlegroepen**.** In vergelijking met eigen controle patiënten rapporteerden NFMA patiënten een verminderde KvL in 18 van de 21 subschalen, craniofaryngioom patiënten in 11 van de 21 subschalen. Ook in vergelijking met literatuurcontroles, laten NFMA patiënten (in 10 van de 21 subschalen) en craniofaryngioom patiënten (5 van de 21 subschalen) een verminderde KvL zien. Dit onderstreept de veronderstelde goede gezondheidsstatus bij controles die door patiënten zijn verzameld (73).

Bij zowel NFMA alsook craniofaryngioom patiënten zijn alle items die betrekking hebben op energie en vermoeidheid afwijkend **(hoofdstuk 6 en 7)**. Daarnaast wordt in beide patiëntengroepen een verminderde fysieke activiteit, mobiliteit en functioneren gevonden. Lineaire regressie analyse toont de aanwezigheid van multipele hypofysaire deficiënties (NFMA) en verminderde visus (craniofaryngioom) als de voornaamste predictoren voor een verminderde KvL. KvL wordt, in mindere mate, tevens negatief beïnvloed door leeftijd, vrouwelijk geslacht, multipele chirurgische procedures en radiotherapie. De aanwezigheid van multipele hypofysaire insufficiëntie als predictor voor een verminderde KvL (**hoofdstuk 6**), wijst in de richting van de belangrijke rol van de hypofyse functie voor een optimale KvL (56). De intrinsieke imperfecties van hormonale substitutietherapie kunnen leiden tot subtiele fysiologische ontregelingen en daarmee ten grondslag liggen aan de verminderde KvL door hypofyse deficiënties (74).

De 4 ziekte-gerelateerde vragenlijsten die we in de studies hebben gerbuikt, zijn niet ziekte-specifiek. Met andere woorden: de vragenlijsten zijn niet ontwikkeld om KvL te evalueren bij NFMA of cranyofaringoom patiënten, hoewel de NHP vaak gebruikt wordt bij patiënten met hypofyse ziekten. Desondanks vonden we een verminderde KvL in de meerderheid van de subschalen van de MFI-20, de SF-36 en de NHP. Dit lijkt te wijzen op een groot effect van de hypofyse op algemene gezondheid en welbevinden, zowel voor wat betreft het fysieke alsook het psychosociale aspect.

Een beperking van het onderzoek is dat KvL niet direct kan worden gemeten. Het wordt afgeleid uit meerdere vragen die geacht worden het begrip kwaliteit van leven te dekken (71). Omdat KvL niet direct gemeten wordt, maar afgeleid middels kwantitatieve scoringssystemen, blijft het mogelijk dat de perceptie van de patiënt betreffende zijn/haar KvL niet overeenkomt met de kwantitatieve uitkomstmaten zoals uit de vragenlijsten naar voren komen.

Klinische implicaties. Ondanks lange-termijn curatie bij patiënten met NFMA en craniofaryngioom is er een duidelijk verminderde kwaliteit van leven bij deze groep patiënten in vergelijkingen met de algemene bevolking (**hoofdstuk 6 en 7**). Dit geldt met name voor fysieke- en vermoeidheidsaspecten. Deze irreversibele effecten van hypofysaire ziekten moeten in ogenschouw worden genomen door artsen bij beoordeling van de patiënten met hypofyse-ziekten.

Mortaliteit bij patiënten met hypofyseadenomen

Verschillende studies hebben een verhoogde mortaliteit aangetoond bij patiënten met hypofysetumoren (49;75-79) en geassocieerde condities zoals hypopituitarisme (50-52). In het merendeel van de studies is de algemene bevolking gebruikt als controlegroep. In **hoofdstuk 5** hebben we gekeken naar de mortaliteitcijfers bij patiënten na transsfenoidale operatie voor hypofysetumoren. Omdat mortaliteit geassocieerd is met zowel algemene aspecten van hypofysetumoren als ook met ziekte specifieke aspecten, hebben we de mortaliteit bij patiënten met de ziekte van Cushing en bij patiënten met acromegalie vergeleken met de mortaliteit bij patiënten met een NFMA. Bij deze laatste patiëntengroep ontbreken ziektespecifieke condities van zowel acromegalie alsook de ziekte van Cushing.

De verhoogde mortaliteit bij patiënten met hypofysetumoren is geassocieerd met verschillende factoren, waarvan sommige ziektespecifiek zijn. Transsfenoidale chirurgie gaat gepaard met een peri-operatieve mortaliteit van ~ 0.9% (80;81). Hypopituitarisme, aanwezig bij het merendeel van de patiënten met een macroadenoom, is geassocieerd met een verhoogde mortaliteit (51;52). Verschillende studies rapporteren een verhoogde cerebro-, en cardiovasculaire sterfte bij patiënten met hypofysetumoren, anders dan de ziekte van Cushing en acromegalie (50;52;77-79). Hoewel de exacte mechanismen waardoor hypopitiuitarisme een verhoogde mortaliteit veroorzaakt niet duidelijk zijn, zijn er suggesties dat hypopituitarisme geassocieerd is met een verhoogd vasculair risicoprofiel (50;82-84). Verschillende auteurs wijzen in dit verband op de rol van onbehandelde groeihormoon deficiëntie (50;85).

Cortisol excess induceert centrale obesitas, diabetes mellitus en hypertensie (86). Deze effecten zijn reversibel na curatie van de ziekte. Desondanks lijkt het zo te zijn dat cortisol overproductie geassocieerd is met een verhoogd cardiovasculair risico, een risico dat mogelijk verhoogd blijft ook als de ziekte in remissie is (87;88). De effecten van cortisol overproductie zijn dus niet compleet reversibel en kunnen daarmee van invloed zijn op de mortaliteit.

De mortaliteit van het gehele cohort was 41% hoger dan in de algemene bevolking, ondanks adequate behandeling **(hoofdstuk 5)**. Daarnaast vonden we dat de mortaliteitscijfers verschillend waren voor de 3 hypofyse ziekten. De gestandaardiseerde mortaliteit ratio (SMR) bij patiënten met een NFMA was 1.24 (95% CI 0.82-1.74). Bij patiënten met de ziekte van Cushing was de SMR 2.39 (95% CI 1.22-3.9). Daarnaast was er een verhoogd relatief mortaliteitsrisico (2.3) bij patiënten met de ziekte van Cushing in vergelijking met NFMA patiënten. Dit wijst op de rol van cortisol bij de verhoogde mortaliteit, te meer daar de medische behandeling van de Cushing en de NFMA groep vergelijkbaar was. Het belang van cortisol wordt onderstreept door het feit dat patiënten met persisterende ziekte van Cushing een hogere mortaliteit hebben dan gecureerde patiënten (89;90).

Klinische implicaties. Het relatieve mortaliteitsrisico is verhoogd bij patinten met de ziekte van Cushing in vergelijking met de NFMA alsook met acromegalie patiënten. Dit impliceert dat cortisol-overproductie een essentiële bijdrage vormt voor de toegenomen sterfte bij patiënten met de ziekte van Cushing.

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CURRICULUM VITAE

Olaf Matthijs Dekkers werd geboren op 23 december 1970 te Schiedam. Na het atheneumdiploma begon hij aan de studie geneeskunde, een drietal jaar later tevens aan de studie wijsbegeerte, beide aan de Vrije Universiteit in Amsterdam. In februari 1999 behaalde hij zijn artsexamen. De studie wijsbegeerte werd in 2001 afgerond met een scriptie over 'de waarheidswaarde in het werk van Frege'.

Vanaf 1999 tot 2001 was hij werkzaam als arts-assistent interne geneeskunde in het Rijnland Ziekenhuis te Leiderdorp. Van 2001 tot 2006 volgde de opleiding tot internist in het Rijnland Ziekenhuis (opleider Dr. F.H.M. Cluitmans) en vervolgens in het Leidsch Universitair Medisch Centrum (opleiders Prof. Dr. A.E. Meinders en Prof. Dr. J.A. Romijn).

In 2004 begon hij zijn wetenschappelijk onderzoek bij Prof. Dr. J.A. Romijn en Dr. A.M. Pereira, hetgeen heeft geleid tot dit proefschrift. Vanaf 2005 tot 1 juli 2006 werd hij opgeleid tot endocrinoloog (opleider Dr. J.W.A. Smit).

Sinds de zomer van 2006 is hij als internist-endocrinoloog werkzaam op de afdelingen Klinische Epidemiologie en Endocrinologie van het Leidsch Universitair Medisch Centrum.