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**CLINICAL INVESTIGATION** **Brain**

# RADIOTHERAPY IS NOT ASSOCIATED WITH REDUCED QUALITY OF LIFE AND COGNITIVE FUNCTION IN PATIENTS TREATED FOR NONFUNCTIONING PITUITARY ADENOMA

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**Purpose: To assess the influence of different treatment modalities on long-term health-related quality of life (HR-QoL) and cognitive problems among patients who had been treated for nonfunctioning pituitary adenoma (NFA).**

**Methods and Materials: Eighty-one patients (49 men and 32 women, aged 55 ± 10 years) with a minimal follow-up period of 1 year after treatment for NFA participated in this cross-sectional study. Sixty-two patients were initially treated by transsphenoidal surgery and 19 by craniotomy. Subsequently, 45 of these 81 subjects (56%) received additional radiotherapy (RT) after surgery because of a tumor remnant or regrowth. All subjects filled in standardized questionnaires measuring HR-QoL, depression, fatigue, and cognitive problems.**

**Results: Patients who underwent additional RT more frequently underwent a craniotomy and were younger at surgery, but not at entering this study. They also used more hormonal substitution. Most HR-QoL domains showed a similar score in patients who underwent RT when compared with patients who did not receive RT. However, vitality and physical functioning proved to be better in RT subjects, and RT subjects also had better scores for depression and physical and mental fatigue (all $p < 0.05$). Some aspects of HR-QoL of patients who have been successfully treated for NFA are reduced compared with the normal population, but this was much more pronounced in the group that did not receive RT. In multivariate analysis, RT remained significantly associated with improved HR-QoL. No differences in cognitive function scores were observed.**

**Conclusion: Postoperative RT in patients with NFA is not associated with reduced quality of life or cognition when compared with surgery alone.** © 2007 Elsevier Inc.

**Nonfunctioning pituitary adenoma, Radiotherapy, Treatment, Quality of life, Cognitive function.**

## INTRODUCTION

Nonfunctioning pituitary adenomas (NFAs) are the most common tumors of the anterior pituitary. Transsphenoidal surgery is the treatment of choice, but complete surgical removal is frequently not achieved. Radiotherapy (RT) is often given as adjuvant treatment in the postoperative period to patients with a tumor remnant or regrowth. Retrospective studies show that RT can effectively reduce the chance of tumor regrowth, as reviewed by several investigators (1–3). Current medical practice involves RT for large postoperative tumor remnants and sequential MRI surveillance for smaller tumors followed by RT in the presence of tumor expansion in many centers (1, 4). The restrictive use of postoperative RT for NFAs is a consequence of absence of regrowth in a number of cases, the excellent local control with RT when applied at time of recurrence, and concerns related to possible long-term side effects (5). The most important of these complications is radiation-induced hypopituitarism and its associated excess mortality (6), though the role of RT per se on pituitary function remains disputed (7). Radiation-induced tumor formation and damage to the optic chiasm are also reported but are considered rare under modern RT dosing schedules (8–10). In addition, neuropsychological changes after pituitary RT have been reported (11–17). However, many studies on this subject are undersized, and results are potentially confounded by inhomogeneous group composition and incomplete hormonal substitution. Further, type and date of surgery, age, and duration

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of follow-up have usually not been taken properly into account to assess the impact of modern RT.

With these considerations in mind, we sought to determine whether the use of RT in the postoperative period has a significant effect on health-related quality of life (HR-QoL) and cognitive function. We report data from a large and homogeneous cohort of patients with NFA.

## METHODS AND MATERIALS

### *Patients*

Patients with histologically proven NFA were eligible for participation in this study if they were between 20 and 70 years of age and if the interval between their last treatment (RT or surgery) and the quality-of-life assessment was at least 12 months. Both surgery and RT were performed in the University Medical Center Groningen, which is a large tertiary referral center for patients with pituitary pathology. To assure accuracy and completeness of our data collection, patients were only recruited for participation if they were still actively followed at our endocrine outpatient clinic. All patients included in this study received surgery as primary treatment, in some cases followed by a second surgical procedure if a large remnant accessible for surgery persisted. Radiotherapy was given postoperatively to patients with a remnant or after evidence of regrowth. Patients with NFA were retrospectively identified by reviewing several different hospital databases on surgery, radiation therapy, and diagnoses at the endocrine clinic. Thus, a total of 90 eligible patients were identified who received primary surgical treatment for NFA in our hospital between January 1963 and January 2005.

Questionnaires on quality of life and cognition, use of medication, presence of comorbidity, and social status were sent to all patients by mail. Use of medication and presence of comorbidity was also confirmed by investigation of the medical charts. Laboratory results from the last visit (*i.e.*, $<1$ year earlier) to the outpatient clinic were used. Written informed consent was obtained from all subjects.

### *Questionnaires*

*RAND 36.* Health-related quality of life was measured with the RAND 36 (which is identical to the 36-item short form health survey [SF36]). This questionnaire contains 36 questions that record several dimensions of general well-being during the previous 4 weeks. The items are formulated as statements or questions with Likert scale response options. The 36 questions are organized into eight scales (physical functioning, physical problems, bodily pain, general health, vitality, social functioning, emotional problems, and mental health) that are linearly converted to a scale of 0 to 100. The first three parameters measure physical health, the last three parameters measure mental health, and the general health and vitality scales are sensitive to both physical and mental health outcomes. Higher scores represent better quality of life (18). Normative data by age are available for the Dutch population (19).

*Multidimensional Fatigue Inventory-20.* The Multidimensional Fatigue Inventory-20 (MFI-20) records fatigue and contains 20 statements, organized into five scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue), with a maximum score of 20 on each subscale (20). Higher scores indicate a higher level of fatigue or impairment. Dutch normative data were derived from Smets *et al.* (21).

*Hospital Anxiety and Depression Scale.* The Hospital Anxiety and Depression Scale (HADS) consists of 14 items pertaining to anxiety and depression (22). Each item is scored as a number, with a maximal score for each subscale (anxiety or depression) of 21. Higher scores indicate more severe anxiety or depression. A score of 6 or higher on the depression scale or 7 or higher on the anxiety scale indicates clinical depression or anxiety. Dutch normative data were derived from Spinhoven *et al.* (23)

*Cognitive Failures Questionnaire.* The Cognitive Failures Questionnaire is a measure of everyday cognitive problems. This 25-item questionnaire measures failures in perception, memory, and action in everyday life. The total score ranges 0–100, with higher scores reflecting more cognitive problems (24, 25)

### *Laboratory assays*

Plasma insulin-like growth factor-1 (IGF-1) was measured by radioimmunoassay after acid-ethanol extraction (Nichols Institute of Diagnostics, San-Juan Capistrano, CA). Age-adjusted $Z$ scores of plasma IGF-1 were calculated using values obtained in healthy subjects. Plasma cortisol was measured by radioimmunoassay (Elecsys 2010; Roche Diagnostics, Basel, Switzerland). An automatic immunoassay (PerkinElmer Life Sciences, Groningen, The Netherlands) was used to determine free T4.

### *Statistical analysis*

Differences were assessed with $t$ tests (for continuous variables) or chi-square tests (for categoric variables). An $\alpha$ level of 0.05 was used for determining statistical significance. When differences between groups reached statistical significance, the magnitude of the effects was determined by Cohen's $d$, a commonly used measure for effect size (26). A value of $\pm 0.5$ was considered the medium effect size. Multiple linear regression was used to determine associations between measures of quality of life, cognitive function, treatment modalities, and demographic characteristics. Backward linear regression modeling was applied using a $p$ value $<0.04$ for entry and a $p > 0.05$ for removal of the selected variables.

## RESULTS

Ninety patients were eligible and were sent questionnaires on quality of life, mood, and cognition. Eighty-one patients (49 men and 32 women, aged 55 $\pm$ 10 years) returned all questionnaires (response rate, 90%). Sixty-two had been operated by the transsphenoidal route and 19 by craniotomy. Fourteen patients had needed a second surgical intervention. Subsequently, 46 of 81 subjects received additional RT after surgery because of a tumor remnant or regrowth. Average time between surgery and RT was approximately 8 months. Conventional external beam RT was administered in a daily dosage of 1.8–2.0 Gy, resulting in a total dose of 45–50 Gy, using a two-field opposed lateral technique or a three-, four-, or five-field technique. All radiation treatment fields were applied daily, five times per week, with an overall duration of 35 days. In the time period 1963–1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose. From 1991 onward it was prescribed at a central point in the tumor, according to the recommendations of the International Commission on Radiation Units and Measurements.